# Gastrobio

*the establishment and use of a registry for patients with inflammatory bowel disease*

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# GASTROBIO: THE ESTABLISHMENT AND USE OF A REGISTRY FOR PATIENTS WITH INFLAMMATORY BOWEL DISEASE

**BY**
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# GASTROBIO: THE ESTABLISHMENT AND USE OF A REGISTRY FOR PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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1. Jensen-Fangel S, **Larsen L**, Thomsen HF, Nielsen LP, Black FT, Obel N. Behandling af hiv- og aids patienter med proteaseinhibitor og to nucleosidanaloger. Ugeskrift for Læger 1999; 161: 1751-4.
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9. **Larsen, L**, Jess, T, Drewes AM, Dige, A, Fallingborg, J, Jacobsen, BA, Aagaard, B, Agnholt J. Premedication With Corticosteroids Does Not Impact Pharmacokinetics of Infliximab in IBD Irrespective of Azathioprine Co-Treatment. *Eur J Gastroenterol Hepatol.* 2019; [Epub ahead of print]
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11. **Larsen L**, Drewes AM, Fallingborg J, Jacobsen BA, Karzoun DS, Poulsen HB, Jess T. Infliximab Induction Without Maintenance Therapy in Crohn's Disease Patients with Benign Prognosis: A Real Life Population-Based Cohort Study, in preparation

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In the text, the papers are referred to with their roman numerals.

I. **Larsen L**, Drewes AM, Fallingborg J, Jacobsen BA, Jess T. Touch screens as a tool in patient care in the IBD outpatient clinic. *Scand J Gastroenterol*. 2016;51(9):1106-1110. doi:10.1080/00365521.2016.1174879

II. **Larsen L**, Drewes AM, Broberg MCH, et al. Changing Infliximab Prescription Patterns in Inflammatory Bowel Disease: A Population-Based Cohort Study, 1999-2014. *Inflamm Bowel Dis*. 2018;24(2):433-439. doi:10.1093/ibd/izx038

III. **Larsen, L**, Jess, T, Drewes AM, Dige, A, Fallingborg, J, Jacobsen, BA, Aagaard, B, Agnholt J. Premedication With Corticosteroids Does Not Impact Pharmacokinetics of Infliximab in IBD Irrespective of Azathioprine Co-Treatment. *Eur J Gastroenterol Hepatol.* 2019 [Epub ahead of print]

The three papers are reprinted in the appendix at the end of the thesis with the permission of the publishers.

# ENGLISH SUMMARY

The emerging possibilities of treating the inflammatory bowel diseases (IBD), Crohn's disease and ulcerative colitis, with biologics towards the end of the 1990's, tended to revolutionize the management of patients. The new biologics were, however, expensive, and it became essential to be able to monitor the clinical efficacy, the health economic burden, and the real-life effects of these medications. Therefore, in Denmark, it became mandatory to register information on treatment with biologics for IBD in a national quality database.

At Aalborg University Hospital, a former population-based cohort database contained information on all IBD patients diagnosed and followed through 1978-2002 in the North Denmark Region. By 2014, this database was no longer operational and there was only scarce updating of patients. The need for at new database with the ability to include updated information on diagnosis, phenotypes, disease course and treatment as well as patient reported outcomes became evident, in particular to provide clinicians with a continuously updated overview of treatments and effects, and optimally, this database should also be able to report to the national quality database for treatment with biologics and provide the basis for observational research and recruitment for trials. The PhD study deals with the establishment of such a database and the use of it.

The solution became GASTROBIO, a web-based registry for clinical registration of patient characteristics and patient management - with associated touch screens, where patients register their symptoms before each consultation (being it with a physician or a nurse) and before every infusion of biologics. These touch screen registrations, which are validated quality of life and disease activity scores, as well as information on side effects, smoking habits, and weight, are immediately available for the doctors and nurses, enabling discussion of patient reports during the visit. All in all, the database gives the staff an overview of the patient's disease history, including disease extent, medications, endoscopies, laboratory data, family history, height, and weight together with these patient reported outcomes. Thus, GASTROBIO provides a tool for clinical management of patients, for extensive research possibilities (which are enhanced after all information from the previous database has been migrated to GASTROBIO), and the database is fully compatible with and delivers monthly data to the national quality registry for treatment with biologics, with no extra effort or double registering for the staff.

During the establishment of GASTROBIO, three specific questions emerged: 1) Is it feasible to set up touch screens in the outpatient clinic?, 2) Can we assess real life use of the biological drug, infliximab, during the first 16 years post marketing?, and 3) Are we able to use the database to identify eligible patients for the study of a

specific clinical question? This led to the three projects upon which the PhD is based.

In the first study, we evaluated the validity of touch screens in the outpatient clinic (as opposed to paper questionnaires), showing good feasibility and optimization of data completeness. This led to a change in clinical practice from using paper questionnaires for patients receiving biological treatment and inconsistent questioning of symptoms by doctors and nurses to consistent registration of each patient's symptoms on the touch screens upon arrival to the clinic. Today, the touch screens are operational and constitute an important part of the clinical management of IBD patients at Aalborg University Hospital.

In the second study, we conducted a real-life study of infliximab use during the first 16 years post-marketing in the North Denmark Region. We demonstrated a change in prescription patterns over time. This study suggested that patients with ulcerative colitis today are younger at first prescription of infliximab than in previous years, that patients with Crohn's disease now tend to have a shorter time from diagnosis to first treatment with a biologic, and that there is a general tendency towards longer duration of treatment today as compared to previous years.

In the third study, we wanted to evaluate the effect of premedication with corticosteroids before infliximab treatment on the formation of antibodies towards infliximab, on infliximab trough levels, and on the elimination rate of infliximab. For a longer period, this question remained unanswered at the Department of Gastroenterology at Aalborg University Hospital, where premedication with corticosteroids was administered routinely. We were able to use GASTROBIO for identification of patients eligible for this study to facilitate recruitment. This study was conducted in collaboration with doctors at Aarhus University Hospital, where premedication was not administered routinely. We were not able to show any effect of premedication and therefore this routine has now been changed in Aalborg.

Collectively, the three studies contribute to showing that it is feasible and beneficial to establish a database with clinical measures and patient reported outcomes for the clinical management of patients with inflammatory bowel diseases, for observational research, for identification of patients for trials, and for data transfer to a mandatory national quality database.

# DANSK RESUME

Med muligheden for at behandle de inflammatoriske tarmsygdomme Crohns sygdom og colitis ulcerosa med biologiske lægemidler i slutningen af 1990'erne, er der sket en revolutionerende forandring i behandlingsmulighederne for disse sygdomme. De nye lægemidler er imidlertid dyre, og samtidig med et ønske om at kunne følge behandlingseffekt klinisk og i forskningssammenhæng har der været et ønske om at have overblik over økonomien både på de enkelte afdelinger, men også i større samfundssammenhæng. Deraf kom også kravet i Danmark om en kvalitetsdatabase vedrørende brugen af disse lægemidler.

På Aalborg Universitetshospital havde man ajourført alle regionens patienter med inflammatoriske tarmsygdomme fra 1978 til 2002 i en database, der ikke længere var funktionel. I 2014 var der ikke meget systematisk registrering i det gamle format, og man følte et behov for en ny database, der kunne inddrage patienternes symptomer i form af patient rapporterede oplysninger, samtidig med at klinikeren kunne få et hurtigt overblik over patientens behandling og effekt. Samtidig var det ønsket, at databasen skulle levere data til den nationale kvalitetsdatabase. Ph.d.-studiet omhandler etableringen af en sådan database og anvendelsen af den.

Løsningen blev GASTROBIO, der er en web-baseret database, som har tilknyttede touch skærme, hvor patienten rapporterer sine symptomer inden hver konsultation hos lægen eller sygeplejersken og inden hver infusion af biologisk medicin. Patientens indtastninger på touch skærmene, herunder validerede livskvalitet og sygdomsaktivitetsscores, samt bivirkningsregistrering, rygevaner, og vægt, er umiddelbart tilgængelige for sundhedspersonalet efterfølgende. Således kan patientens indrapporteringer diskuteres direkte i forbindelse med konsultationen. Desuden giver databasen et overblik over patientens sygdomsvarighed, udbredelse, medicin, endoskopier, paraklinik, familiære dispositioner, højde, vægt osv. Databasen er således et værktøj til det kliniske arbejde. Den gamle database kunne overføres til GASTROBIO, og dermed var den tidligere erhvervede viden bevaret, hvilket styrkede forskningsmulighederne. Nogenlunde samtidig med etableringen af GASTROBIO blev der nedsat en styregruppe med ansvar for tilblivelsen af en kvalitetsdatabase på området. GASTROBIO er fuldt kompatibel med kvalitetsdatabasen, og transmitterer data månedligt uden ekstra arbejde og dobbeltindtastninger for personalet.

I forbindelse med etableringen af GASTROBIO opstod følgende tre spørgsmål: 1) Er det muligt at overgå til touch skærme i ambulatoriet? 2) Hvordan er det gået i det kliniske arbejde med behandlingen med det biologiske lægemiddel infliximab de første 16 år efter registrering? 3) Kan vi undersøge et klinisk spørgsmål ved at finde patienter i databasen, som kan indgå?

I det første studie undersøgte vi validiteten af touch-skærme i ambulatoriet frem for papir spørgeskemaer. Vi viste, at det var muligt at bruge touch-skærme, og vi erfarede, at datakompletheden blev optimeret. Tidligere brugte man papirspørgeskemaer til patienter, der fik biologisk behandling, mens øvrige patienter blev spurgt om deres symptomer af lægen med varierende regelmæssighed, men nu udfylder alle patienterne spørgsmålene via touch-skærmene. Touch-skærmene er i brug og en vigtig del af den daglige behandling af patienter med inflammatoriske tarmsygdomme på Aalborg Universitetshospital.

I det andet studie foretog vi en deskriptiv undersøgelse af de første 16 år, infliximab har været på markedet i Danmark og fik bekræftet vores hypotese, at der i løbet af årene er sket en ændring i ordinationen af infliximab. Vi kunne vise, at patienter med colitis ulcerosa er blevet yngre ved første ordination, patienter med Crohns sygdom har kortere tid fra sygdomsdebut til biologisk behandling, og generelt at der er en tendens til, at patienterne får behandlingen i længere tid i de senere år sammenlignet med tidligere år.

I det tredje studie ønskede vi at undersøge, om forbehandling med binyrebarkhormon forud for infliximab behandling kunne reducere antistof-dannelse mod infliximab, kunne øge dalværdier af infliximab og ændre eliminationshastigheden. Det var et spørgsmål, der havde optaget Medicinsk Gastroenterologisk afdeling, Aalborg Universitetshospital, gennem længere tid. Vi kunne bruge GASTROBIO til at identificere de patienter, der var relevante for studiet og på den måde rekruttere patienter. Studiet blev lavet sammen med læger på Aarhus Universitetshospital, hvor man ikke rutinemæssigt giver forbehandling, og vi kunne ikke vise en gunstig effekt af binyrebarkhormon-behandlingen. Det har haft den konsekvens, at man nu er stoppet med at give denne forbehandling rutinemæssigt i Aalborg.

Samlet set bidrager de tre studier til at vise, at det er muligt og nyttigt at etablere en database mhp. monitorering af behandling af inflammatoriske tarmsygdomme, observationel forskning, identifikation af patienter til kliniske forsøg og samtidig overførsel af data til en obligatorisk national kvalitetsdatabase.

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# CHAPTER 1. INTRODUCTION

## 1.1. INFLAMMATORY BOWEL DISEASES

The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are autoimmune diseases with an etiology not fully comprehended. It is generally believed that the etiology is multifactorial. Thus, genetics, environmental and immunogenetic factors, as well as microbiota disequilibrium are most likely involved. The two diseases are on the rise worldwide with the highest incidence and prevalence in the developed countries[1–7]. In Denmark, where the incidence is among the highest in the world, the prevalence is not well established, but the latest estimate is as high as 52.730 patients. Of these, 17.530 have CD and 35.200 have UC[8].

The first accounts of what was later known as Crohn's disease are believed to date back to the 1700s[9], but not until 1932 came the first actual description of the disease when Dr. Bernard Crohn and colleagues at Mount Sinai University described 14 cases of regional ileitis with similar clinical and pathological findings[10]. This disease entity was later named after Dr. Crohn. Ulcerative colitis is less well described historically. Descriptions of bloody diarrhea and dysentery are found in antiquity[11]. The first case description is credited to Wilks in 1859[12], but was later found to be Crohn's colitis[13]. However, in 1875, Wilks and Moxon made a detailed description of a syndrome of simple ulcerative colitis[14]. In 1960, Lockhart-Mummery and Morson made the phenotypic distinction between the two disease entities[15].

The diseases are chronic, relapsing and affect many aspects of the patient's life. IBD is associated with marked morbidity, and even a slightly elevated mortality for Crohn's patients[16]. There is no cure, and before the mid 1900s, therapy was primarily surgical. From the 1950's to the 1990's, the evolution of treatment for IBD was slow. Sulfasalazine was first used in the treatment of ulcerative colitis in 1941[17]. It was a stroke of luck that lead to the establishment of the drug's effect, as it was administered for patients in rheumatology for arthralgia and turned out to also reduce their diarrhea[11]. In 1977, it was discovered that it was 5-aminosalicylate (5-ASA) that was responsible for the positive effect on UC[18]. In a randomized controlled trial from 1955, Truelove and Witt showed that hydrocortisone was highly effective in ulcerative colitis[19]. Corticosteroids were also shown to have effect in CD[20], but they were generally unfit for prophylactic use, and unfortunately they proved to be associated with a high level of relapse and steroid-dependency[21]. In 1980, the for other indications well-known drugs azathioprine (AZA) and 6-mercaptopurine (6-MP) were shown to be able to sustain remission[22] in IBD. In 1995, Feagan and colleagues further showed that methotrexate was effective in improving symptoms and reducing the need for prednisolone[23], and in maintaining remission[24]. However, for patients with intolerable side effects to or lack of effect of

these drugs, there was no alternative to surgery. Therefore, a need for new therapies was evident, and in the late 1990's, a new era in the treatment of IBD began with the introduction of anti tumour necrosis factor alpha (anti-TNF) therapy.

## 1.2. BIOLOGICAL THERAPY

The first available biologic drug for IBD was infliximab (IFX). It was registered in the United States in 1998, and in Denmark in 1999. IFX is a chimeric monoclonal IgG1 antibody being a combination of 75% human and 25% murine antibody amino acid sequences. This antibody targets anti-TNF alpha, which is a pro-inflammatory cytokine, by blocking its ability to interact with the TNF receptors, thus inhibiting the production of other pro-inflammatory cytokines involved in the systemic inflammatory response. IFX also blocks the anti-TNF mediated enhancement of leukocyte movement or migration from the blood vessels into the tissues as well as the release of adhesion molecules[25–27]. IFX thus causes a reduction of inflammation in systemic immune response by specifically blocking the TNF-alpha receptor. IFX is termed a biological drug, because it is manufactured from recombinant purified DNA, in this case from mouse and human antibodies.

The administration is intravenous, as the drug would otherwise be destroyed by the digestion tract. The dosage is 5-10 mg/kg initially at week 0, 2 and 6, and maintenance therapy every 8th week if indicated[27].

Studies on efficacy and safety of IFX especially in clinical trials are numerous[26,28,29]. Large nationwide population based cohort studies have addressed both the risk of infections and cancer[30,31]. However, in order to optimize the conduct of real-life studies on the use of biologics in unselected patient cohorts, a clinical database with recording of phenotypic features as well as patient reported outcomes (PROs) is pivotal.

## 1.3. THE ESTABLISHMENT OF THE DATABASE

At the Department of Gastroenterology and Hepatology at Aalborg University Hospital, the IBD team had previously collected subsequent data on IBD patients from 1978 and onwards for research purposes in the so-called DARIBO registry. These data have been reported in several papers[1,2,32,33]. However, while the data on all patients in the Region were updated by 2002, the following years showed a declining completeness of the data, and by 2014 only a small percentage of new IBD patients were registered. Moreover, patient histories were not updated.

Along with the new costly biological treatments, the need for a database re-emerged. As technology advanced, the objective for a tool to monitor the treatment of the individual patient as well as for research purposes had become feasible. The solution became a database created by the PhD student in collaboration with Zitelab Aps,

hence forming the basis for the present PhD project. The underlying IT solution was an open source web-based technology. It was based on Plone (www.plone.org) in combination with R (www.r-project.org) and MySQL (www.mysql.org), which enables rapid development circles without any licensing costs or other economic bindings. It was named GASTROBIO.

As Aalborg University hospital was (and still is) the only hospital in the North Denmark Region (~583,000 inhabitants) to offer biological therapy to IBD patients, initially GASTROBIO was supposed to be a registry for patients receiving biological therapy. However, a large amount of data was already available in DARIBO and it was therefore decided that the new database should comprise all the IBD patients from DARIBO (1978-2002) and all IBD patients diagnosed and treated thereafter.

The database was aimed to be a tool for the clinician as well as for the patient, so that data collection in the future would be easier and more regular. Thus, the database was built up with a variety of relevant information about the patient.

Along with this, the PhD student introduced touch screens in the outpatient clinic as online questionnaires for patients to answer questions about their symptoms and general well-being before each consultation or biological treatment.

*1-1 Touch screens at the IBD outpatient clinic at Aalborg University Hospital*

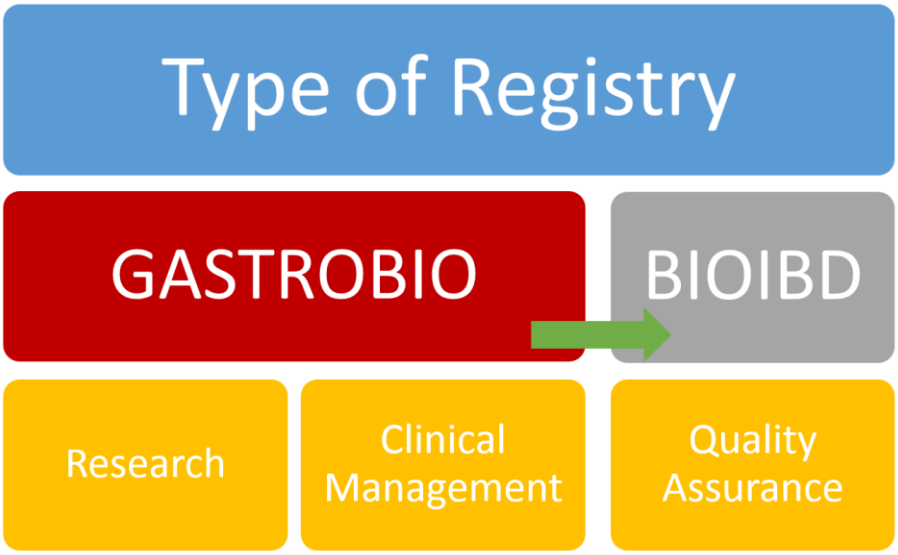
The establishment of this database and its use became the basis for this PhD thesis.

## 1.4. CLINICAL MANAGEMENT, RESEARCH AND QUALITY ASSURANCE

The PhD study covers clinical management and research while quality assurance is a separate entity.

The database is fully able to handle quality assurance, but a National Clinical Quality registry for biological therapy (BIOIBD) with funding from the Danish Regions has been established under the Centre of Competence for Nationwide Clinical Registries[34]. The PhD student is a member of the steering committee of this registry and has secured the compatibility of GASTROBIO to BIOIBD. Therefore, at Aalborg University Hospital, the clinicians spend no extra time entering data into BIOIBD, as GASTROBIO can readily transfer the data required.

It is mandatory to report to the national registry. Figure 1 outlines the differences in types of registries.




*1-2 Type of Registry*

## 1.5. RESEARCH POSSIBILITIES

Three different initial research themes emerged in relation to the establishment of GASTROBIO.

1) Studying the validity of the touch screen questionnaires

2) Describing the patients receiving biological treatment in the database

3) Using the database for identification of patients for intervention studies

## 1.6. VALIDATION OF TOUCH SCREENS

A study from 2010 had shown that touch screens in rheumatology generate valid data, are well accepted by the patients, and display a number of advantages compared to paper versions[35]. This study validated touch screens for patients with rheumatoid arthritis, psoriasis arthritis, and ankylosing spondylitis in the Danish National Rheumatology Registry, DANBIO. Touch screens have been evaluated in several other studies. De Bree and colleagues suggested that touch screens collecting health related quality of life and distress data on head and neck cancer patients were functional for clinical and scientific documentation[36]. In 2008, Ramachandran and colleagues tested a visual analog scale on paper and touch screens in random subjects in the Tucson metropolitan area in Arizona, USA[37]. They found the touch screen mode to have an acceptable agreement with the paper mode.

Touch screens in the outpatient clinic at the Department of Gastroenterology and Hepatology at Aalborg University Hospital where patients tap the answers to their symptomatology, general wellbeing, weight, and smoking habits at every visit have been operational since January 15, 2015.

Previously in Aalborg, the physician asked the patients these questions, but not consistently. When the patients came for biological therapy, they filled out a questionnaire in paper.

## 1.7. DESCRIPTIVE STUDY OF THE USE OF INFLIXIMAB

Several studies on efficacy and side-effects in regards to biological agents have been published[26,28,45–51,29,38–44]. It has thus been shown that IFX is both effective and safe. However, large population based studies on the number of patients being treated with the individual drugs, the patient category, and the number of patients who terminate therapy for different reasons are rare. It has been addressed in one study by Caspersen and colleagues from 2008, concluding that IFX is safe and generally well tolerated, although rare but severe adverse events occurred[49]. This study dates back to the beginning of the biological era from 1999-2005, when the use of these medications was limited to a small subset of patients. Other studies have shown a tendency towards patients being treated with biological drugs at a younger age in recent years[52,53], but as the experience with prescribing these drugs increase, this may change over time. Desai and colleagues also suggested that patients older than age 60 were more likely to terminate the biological therapy earlier than younger

patients[52]. Pressman and colleagues could already in 2008 show that the use of infliximab had increased substantially during the first 10 years post-marketing[53].

Since the introduction of IFX at Aalborg University Hospital in 1999, it has been evident that the use of the drug has increased every year. Therefore, there was a presumption that a changing prescription pattern had emerged. With the unique data collection on all patients receiving IFX in a geographically well defined population, it was now feasible to undertake a large population based descriptive study of the first 16 years of administration of IFX in the North Denmark Region with the detailed knowledge of treatment duration and causes for discontinuation.

## 1.8. IDENTIFICATION OF PATIENTS FOR AN INTERVENTION STUDY

With the introduction of IFX, consisting of 25% murine protein, came an awareness of allergic reactions. Antibodies towards IFX were acknowledged and believed to be responsible for both loss of clinical effect[54], but also possibly infusion reactions[55]. It is well known that infusion reactions do not occur during the first infusion, but increases in incidence during the subsequent infusions. In the ACCENT I randomized trial on maintenance therapy with IFX for CD in Lancet in 2001, Hanauer and colleages showed that the lowest incidence of infusion reactions occurred in the group of patients who received both steroids and immunosuppressives[28].

A long standing unanswered question for the physicians at Aalborg University Hospital, was the effect of premedication in IFX therapy. In Denmark, there have been different approaches to premedication with corticosteroids before infliximab infusions. Some centers have done it consistently, some centers have never done it, and some centers have done it when the patient is not naïve to infliximab.

The theory that the risk of allergic reactions is reduced by premedication with corticosteroids has been the reason for this practice at the Department of Gastroenterology and Hepatology at Aalborg University Hospital. All patients receiving IFX in Aalborg have received premedication with corticosteroids from 1999 to 2017. However, at Aarhus University Hospital this was not the case, and therefore, with the newly established database, it was now possible to conduct a study between the two centers.

# CHAPTER 2. OBJECTIVES

## 2.1. OBJECTIVE PAPER I

The overall objective of this study was to examine the feasibility of introducing patient involvement through touch screens at the outpatient clinic.

## 2.2. OBJECTIVE PAPER II

With this study, we aimed:

1. To present an overview of real-life use of IFX in a population-based cohort, the North Denmark Region, from 1999-2014, comprising
    a. Characteristics for the patients: gender, age, weight, height, smoking habits, disease duration, disease extension, family history of IBD
    b. Indications for biological therapy in the cohort
    c. Causes for termination of biological therapy, i.e., allergic reactions, side effects, surgery, death

    in order to describe changes in prescription patterns.

## 2.3. OBJECTIVE PAPER III

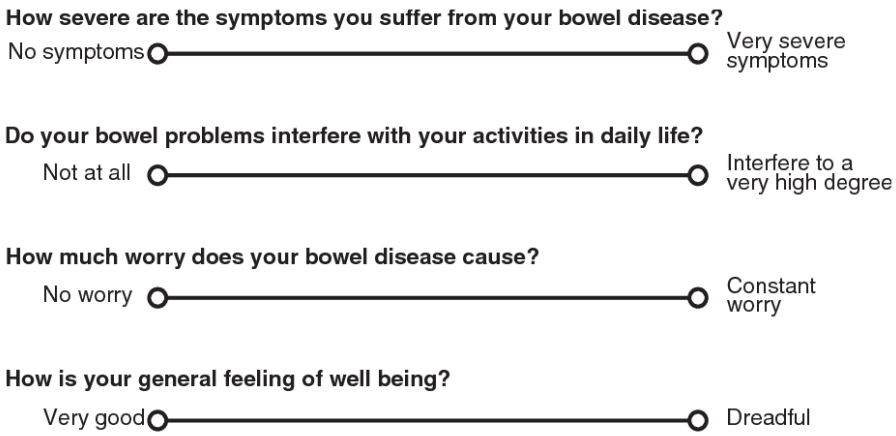
The third study had the objective to use the database to easily identify patients for research.

The objective of this study was to evaluate pretreatment with corticosteroids before infusion with infliximab in patients with Crohn's disease in order to determine the effect on IFX trough levels, the time of IFX elimination, and anti-TNF alpha antibody level in the blood.

# CHAPTER 3. MATERIALS AND METHODS

## 3.1. GASTROBIO

The database contains variables regarding type of disease (UC, CD, IBD-unclassified, or other), family history, treatment (biologics, standard treatment), laboratory results (C-reactive protein, hemoglobin, albumin, fecal calprotectin), side effects, smoking, age, height, surgery, pregnancies, endoscopies, extent of disease, and activity scores. The Short Health Scale (SHS)[56,57] and Short Clinical Colitis Activity Index (SCCAI)[58] were used for patients with UC and SHS and Harvey Bradshaw Index (HBI)[59] for patients with CD.




*3-1 The English version of the Short Health Scale*

| Symptom | Score |
|---|---|
| | |
| **Bowel frequency (day)** | |
| 1-3 | 0 |
| 4-6 | 1 |
| 7-9 | 2 |
| >9 | 3 |
| | |
| **Bowel frequency (night)** | |
| 0 | 0 |
| 1-3 | 1 |

| | |
|---|---|
| 4-6 | 2 |
| | |
| **Urgency of defacation** | |
| None | 0 |
| Hurry | 1 |
| Immediately | 2 |
| Incontinence | 3 |
| | |
| **Blod in stool** | |
| None | 0 |
| Trace | 1 |
| Occasionally frank | 2 |
| Usually frank | 3 |
| | |
| **General well-being** | |
| Very well | 0 |
| Slightly below par | 1 |
| Poor | 2 |
| Very poor | 3 |
| Terrible | 4 |
| | |
| **Extracolonic manifestations** | 1 per manifestation |
| Arthritis | |
| Uveitis | |
| Erythema nodosum | |
| Pyoderma gangrenosum | |

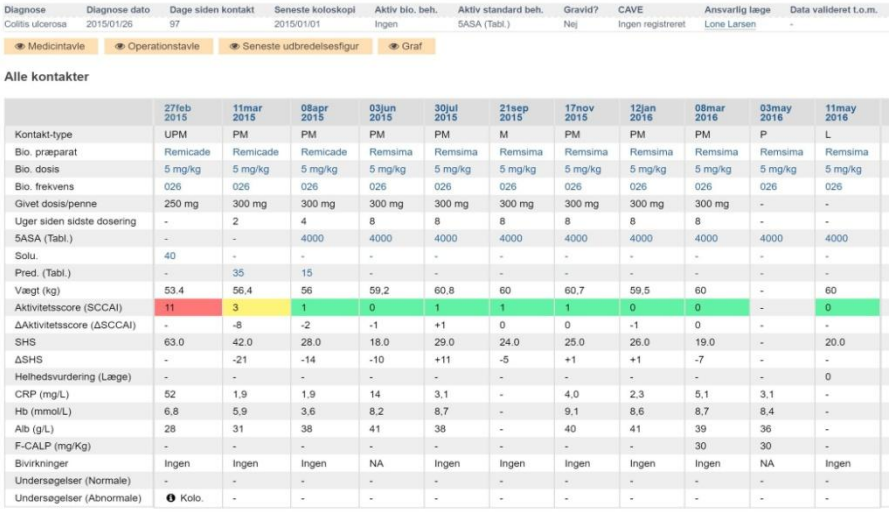
*Table 3 The Short Clinical Colitis Activity Index*

| **Symptom** | **Score** |
|---|---|
| | |
| **General well-being (yesterday)** | |
| Very well | 0 |
| Slightly below par | 1 |
| Poor | 2 |
| Very poor | 3 |
| Terrible | 4 |
| | |
| **Abdominal pain (yesterday)** | |
| None | 0 |
| Mild | 1 |
| Moderate | 2 |
| Severe | 3 |
| | |
| **Number of liquid stools per day (yesterday)** | |
| If no stomi | 1 per liquid stool |
| | |

| **Abdominal mass** | |
|---|---|
| None | 0 |
| Dubious | 1 |
| Definite | 2 |
| Definite and tender | 3 |
| | |
| **Extraintestinal manifestations** | 1 per manifestation |
| Arthralgia | |
| Uveitis | |
| Erythema nodosum | |
| Aphthous ulcers | |
| Pyoderma gangrenosum | |
| Anal fissure | |
| New fistula | |
| Abscess | |

*Table 4 The Harvey Bradshaw Index*

The data are collected real-time, as patients stop by the touch screens at every visit, both for a consultation with at doctor or a nurse, but also before biological treatment. The result from the touch screen is immediately available in the database which the doctors and nurses access using a web-browser.



| Diagnose | Diagnose dato | Dage siden kontakt | Seneste koloskopi | Aktiv bio. beh. | Aktiv standard beh. | Gravid? | CAVE | Ansvarlig læge | Data valideret t.o.m. |
|---|---|---|---|---|---|---|---|---|---|
| Colitis ulcerosa | 2015/01/26 | 97 | 2015/01/01 | Ingen | 5ASA (Tabl.) | Nej | Ingen registreret | Lone Larsen | - |

Medicintavle | Operationstavle | Seneste udbredelsesfigur | Graf

**Alle kontakter**

| | 27feb 2015 | 11mar 2015 | 08apr 2015 | 03jun 2015 | 30jul 2015 | 21sep 2015 | 17nov 2015 | 12jan 2016 | 08mar 2016 | 03may 2016 | 11may 2016 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Kontakt-type | UPM | PM | PM | PM | PM | M | PM | PM | PM | P | L |
| Bio. præparat | Remicade | Remicade | Remicade | Remsima | Remsima | Remsima | Remsima | Remsima | Remsima | Remsima | Remsima |
| Bio. dosis | 5 mg/kg | 5 mg/kg | 5 mg/kg | 5 mg/kg | 5 mg/kg | 5 mg/kg | 5 mg/kg | 5 mg/kg | 5 mg/kg | 5 mg/kg | 5 mg/kg |
| Bio. frekvens | 026 | 026 | 026 | 026 | 026 | 026 | 026 | 026 | 026 | 026 | 026 |
| Givet dosis/penne | 250 mg | 300 mg | 300 mg | 300 mg | 300 mg | 300 mg | 300 mg | 300 mg | 300 mg | - | - |
| Uger siden sidste dosering | - | 2 | 4 | 8 | 8 | 8 | 8 | 8 | 8 | - | - |
| 5ASA (Tabl.) | - | - | 4000 | 4000 | 4000 | 4000 | 4000 | 4000 | 4000 | 4000 | 4000 |
| Solu. | 40 | - | - | - | - | - | - | - | - | - | - |
| Pred. (Tabl.) | - | 35 | 15 | - | - | - | - | - | - | - | - |
| Vægt (kg) | 53.4 | 56,4 | 56 | 59,2 | 60,8 | 60 | 60,7 | 59,5 | 60 | - | 60 |
| Aktivitetsscore (SCCAI) | 11 | 3 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | - | 0 |
| ΔAktivitetsscore (ΔSCCAI) | - | -8 | -2 | -1 | +1 | 0 | 0 | -1 | 0 | - | - |
| SHS | 63.0 | 42.0 | 28.0 | 18.0 | 29.0 | 24.0 | 25.0 | 26.0 | 19.0 | - | 20.0 |
| ΔSHS | - | -21 | -14 | -10 | +11 | -5 | +1 | +1 | -7 | - | - |
| Helhedsvurdering (Læge) | - | - | - | - | - | - | - | - | - | - | 0 |
| CRP (mg/L) | 52 | 1,9 | 1,9 | 14 | 3,1 | - | 4,0 | 2,3 | 5,1 | 3,1 | - |
| Hb (mmol/L) | 6,8 | 5,9 | 3,6 | 8,2 | 8,7 | - | 9,1 | 8,6 | 8,7 | 8,4 | - |
| Alb (g/L) | 28 | 31 | 38 | 41 | 38 | - | 40 | 41 | 39 | 36 | - |
| F-CALP (mg/Kg) | - | - | - | - | - | - | - | - | 30 | 30 | - |
| Bivirkninger | Ingen | Ingen | Ingen | NA | Ingen | Ingen | Ingen | Ingen | Ingen | NA | Ingen |
| Undersøgelser (Normale) | - | - | - | - | - | - | - | - | - | - | - |
| Undersøgelser (Abnormale) | Kolo. | - | - | - | - | - | - | - | - | - | - |

*3-2 Patient board in GASTROBIO. Colors are defined by the total activity score as an indication of severity of disease activity*

For research purposes, a search of the database can be made for relevant variables and dates.

### 3.1.1. ETHICAL CONSIDERATIONS

The GASTROBIO registry has been approved by the Danish Data Protection Agency as a Research registry (2008-58-0028) and by the North Denmark Region as a clinical treatment database. The Danish Health Authority has approved the collection of data from patients from the whole North Denmark Region as a continuation of the old (DARIBO) database (3-3013-720/1).

Regarding Paper I, all patients consented to participate. However, according to Danish law, the study did not require further approval from the Ethics Committee.

Regarding Paper III, the Regional Committee on Health Research Ethics approved the study (N-20140003).

### 3.1.2. STATISTICAL APPLICATION

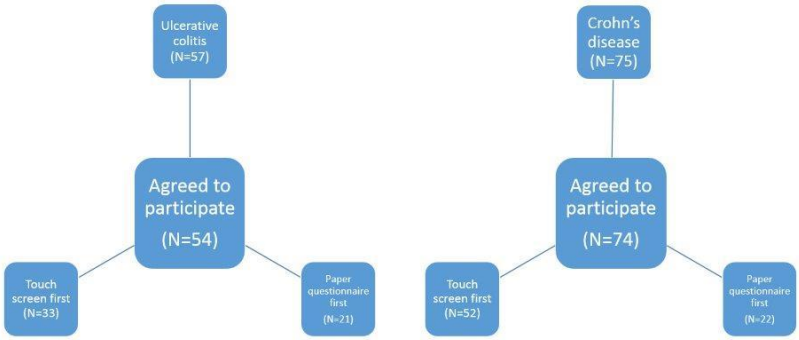
Analyses were carried out using Stata (Stata/IC 12.1 for Windows, www.stata.com). We applied 2-sided tests with corresponding P values, using a significance level of 5%. For further details, please see paragraphs of statistics under the description of each of the three papers.

## 3.2. PAPER I

### 3.2.1. PATIENTS

Over a 30-day period (from 21 August 2015 to 18 September 2015), 57 UC patients and 75 CD patients were invited to participate in this validation study. The patients came to the outpatient clinic for a consultation with a physician or for biological treatment.

They were all asked to fill out the paper questionnaires as well as the touch screen questionnaires. A random group of the patients filled out the paper questionnaires first and the rest used the touch screens first.




*3-3 Patients in the study*

### 3.2.2. QUESTIONNAIRES

Both UC and CD patients received identical questions on weight, smoking habits, and adverse events. UC patients further filled out the SHS scale and SCCAI score while CD patients filled out the SHS scale and HBI score.

The SHS is a visual analog scale and on the touch screens patients were asked to place a mark on the scale. Subsequently the system calculates the score from 0 to 100. However, on the paper questionnaires, patients were asked to give a number between 0 and 100. The questions adding up to the SCCAI and HBI scores were answered by checking off a box with the relevant answer for every question.

### 3.2.3. STATISTICAL ANALYSES

The Spearman correlation coefficient was calculated for the SHS scores, and Bland-Altman plots were used for visualization.

The Kappa-statistic measure of agreement was performed on the SCCAI and HBI scores. This was done both raw and weighted according to disagreements.

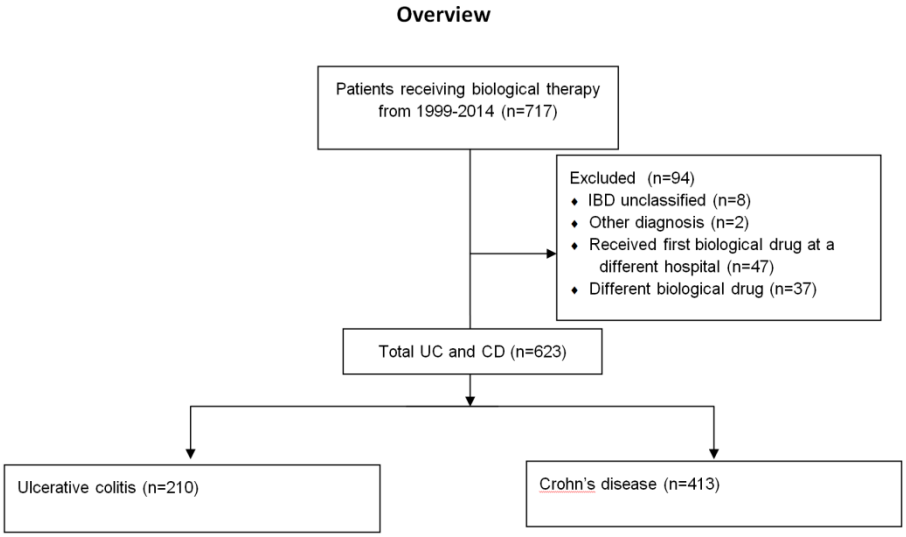
McNemar's exact significance test was used to test for differences in missing data patterns.

## 3.3. PAPER II

### 3.3.1. STUDY POPULATION

All IBD patients treated with infliximab in the North Denmark Region between 1999 and 2014 were included in the study.

Infliximab for CD patients had been administered since 1999 and for UC since 2005 at Aalborg University Hospital.




*3-4 Study population*

### 3.3.2. DEFINITIONS

Indications were divided into "Acute severe UC", "Chronically active UC", "Luminal CD", and "Fistulizing CD".

Disease extent was divided into "Leftsided" and "Pancolitis" for UC patients, and "Upper gastroentestinal disease", "Ileal", "Ileocolonic", and "Colonic disease" for CD patients according to the Montreal classification[60].

The time of exposure was divided into two time periods: 2005-2009 and 2010-2014 for UC patients, and 1999-2009 and 2010-2014 for CD patients.

### 3.3.3. STATISTICAL ANALYSES

Linear regression was performed to assess changes over time. Thus age at exposure and disease duration were analyzed by year of first IFX exposure. In addition, a sensitivity analysis was performed, removing the years 1999-2003.

Changes over time in "Disease extent" and "Indications" were examined between the two time periods using the $\chi^2$ test.

Kaplan-Meier curves were used to evaluate differences in time to discontinuation between the two time periods.

## 3.4. PAPER III

### 3.4.1. STUDY POPULATION

Two groups of CD patients with or without concomitant pre-medication with corticosteroids in maintenance therapy with infliximab for 12 months (12-18 months) from two Danish centers (Aalborg University Hospital and Aarhus University Hospital) participated in this study between 2015 and 2017. All patients were naïve to biologics. In Aalborg, patients eligible for the study were identified in GASTROBIO which made inclusion into the study more effortless.

Premedication (if given) consisted of 40 mg prednisolone administered orally at home on the day before the infusion and 40 mg of methylprednisolone (SoluMedrol®) intravenously right before the infusion.

### 3.4.2. BLOOD SAMPLES

Blood samples were taken before, one hour after and one week after the IFX infusion and IFX concentration analyses were performed. Anti-TNF alpha antibody concentration was analyzed for the blood sample taken before the IFX infusion.

### 3.4.3. STATISTICAL ANALYSES

Linear regression was performed to test for differences in the IFX and IFX antibody concentrations with or without premedication with corticosteroids. Furthermore, tests for interaction were made regarding concomitant azathioprine (AZA) use.

Logarithmic transformation was made in order to obtain normally distributed data regarding IFX concentrations and IFX antibody concentrations, but it was not done for the half-life of IFX as these data were normally distributed. For the data submitted to logarithmic transformation, geometric means and coefficients of

variation were reported, and for the IFX half-life data, means and standard deviations were reported.

# CHAPTER 4. RESULTS

## 4.1. PAPER I

The study included 54 UC patients (52% males), and 74 CD patients (47% males). Sixty-one percent of the UC patients and 70 percent of the CD patients filled out the touch screens first.

Completeness of SHS scores was seen in 46 UC patients (85%) and 59 CD patients (80%).

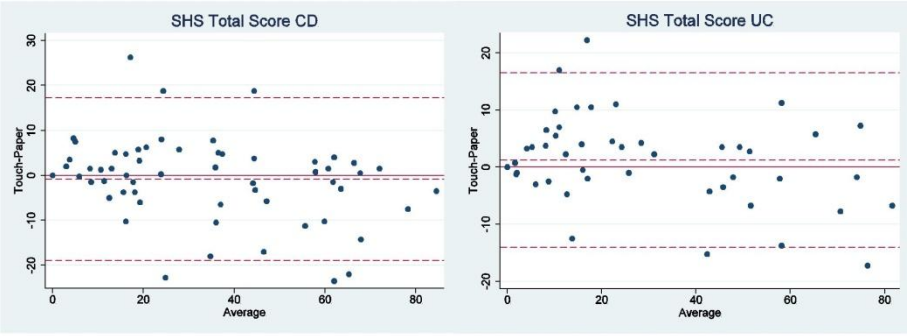
SCCAI scores were complete for 51 UC patients (94%). HBI scores were completed by 62 CD patients (84%).

There were 5 UC patients (9%) and 2 CD patients (3%) above 65 years of age. No separate analyses were made on these patients, but a number of misunderstandings of the questionnaires were reported in connection to these patients.

### 4.1.1. CORRELATION

SHS scores demonstrated a high correlation (Spearman) of 0.92 for both CD and UC regarding SHS on touch screens and SHS on paper. Bland-Altman plots showed no difference between the two modalities.

There was a high agreement (Kappa-statistic measure of agreement) for both SCCAI scores (78% raw, and 98% weighted) and HBI scores (65% raw, and 97% weighted). This indicated that patients gave the same response on the touch screen and on paper.




SHS: Short Health Scale
CD: Crohn's disease
UC: Ulcerative colitis

*4-1 Bland-Altman plots of SHS for UC and CD. The full-drawn line marks the zero value on the ordinate. The dotted horizontal lines mark the mean difference and the limits of agreement*[61].

## 4.2. PAPER II

This study found 717 IBD patients receiving biological therapy in the study period (1999-2014). Of these, 623 patients (210 with UC and 413 with CD) had initiated treatment with IFX as their first biologic. Of the UC patients, 51% were males whereas only 41% of the CD patients were males.

### 4.2.1. AGE AT EXPOSURE

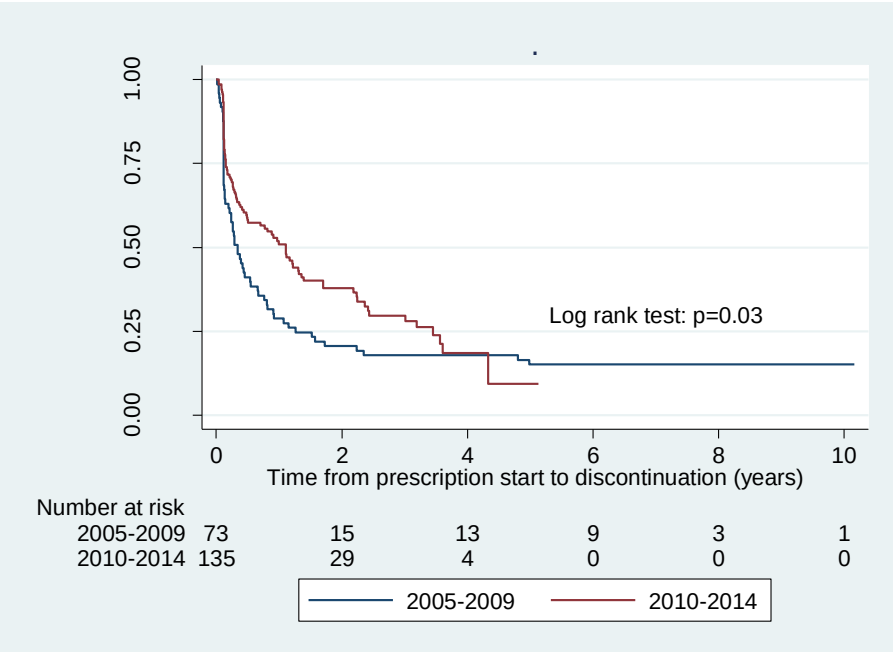
For UC patients, the mean age at first exposure to IFX decreased by 10 months per calendar year during the study period from 2005-2014 (95% CI, -1.58 to -0.03; $P<0.05$). This was not the case for CD patients, nor after removing years 1999-2004 as a sensitivity analysis.

### 4.2.2. DISEASE DURATION

For CD patients, the mean time from IBD diagnosis to first IFX exposure decreased by 7 months per calendar year (95% CI, -0.84% to -0.33%; $P<0.001$), and after removing the first years, thus studying years 2004-2014 only, this time was still decreased by 5 months per calender year (95% CI, -0.72% to -0.01%; $P<0.03$). No change in disease duration before IFX exposure was detected among UC patients.

### 4.2.3. DURATION OF TREATMENT

For UC patients exposed to IFX during 2010-2014, the time from initiation of treatment to discontinuation of treatment increased compared to years 2005-2009. The median interval was 1.11 years compared to 0.34 years (HR 1.42; 95% CI, 1.02 to 1.98; $P = 0.04$).




*4-2 Time from infliximab prescription to discontinuation in a population-based cohort of patients with ulcerative colitis (n = 208)*[62].

## 4.3. PAPER III

A total of 57 patients were included in the study. Of these, 31 received premedication with corticosteroids. In this group, 11 patients (35.5%) were on concomitant immunomodulator therapy with azathioprine, whereas 22 (84.6%) of the 26 patients in the other group received azathioprine. Two patients dropped out of the study before the one week after blood sample.

### 4.3.1. EFFECTS OF PREMEDICATION WITH CORTICOSTEROIDS

This study showed no effect on premedication with corticosteroids on IFX trough levels (geometric mean 7.3 μg/mL vs 5.1 μg/mL with and without corticosteroids, p=0.10), IFX elimination time (10.5 days in both groups, p=0.31), or IFX antibody formation (10.0 AU/ml and 6.7 AU/ml p=0.28). However, independently of corticosteroid premedication, concomitant use of azathioprine was associated with higher IFX trough levels (p=0.023), longer half-life of IFX (p=0.04), and lower IFX antibody concentrations (p=0.004).

# CHAPTER 5. DISCUSSION OF RESULTS

## 5.1. PAPER I

### 5.1.1. FEASIBILITY

In this validation study, we show that it is feasible to introduce touch screens in the IBD clinic.

Among the strengths of this study is patients' familiarity with the questions. The patients already knew the questions of the HBI and SCCAI scores from the paper questionnaires. We therefore consider confounding due to misunderstanding of questions less likely. Also, on paper it is easier to omit an answer. On the touch screen, patients have to acknowledge that they are omitting an answer before being able to proceed. Furthermore, on the touch screens patients have no risk of receiving the wrong questionnaires, whereas when paper questionnaires are handed out by the staff, UC patients could be given CD questionnaires and vice versa. This was seen in the study.

However, some limitations of the study should be addressed. First, the study was undertaken during only one day for the individual patient. Patients were asked to fill out both paper as well as touch screen questionnaires consecutively. Therefore, the results could be positively biased if patients remembered what they just answered. In a study of patients with rheumatological disorders by Schefte and Hetland[35], the same approach was used, whereas in the validation of the SHS in UC by Hjortswang and colleagues[57] and in CD by Stjernman and colleagues[56], the retesting was done after two and four weeks, respectively. This, however, is hardly a feasible approach to IBD patients whose symptoms are likely to change during the course of even a short time. Second, in the HBI score there is a subscore "Abdominal mass". This is supposed to be filled out by the physician, but we let the patient evaluate this subscore. Also, patients with previous surgery were asked to fill out the questionnaires, but HBI is not validated for this group of patients. Third, the visual analog scale had not been used previously on paper in our clinic. Patients were asked to name a number from zero to 100 on the paper questionnaires whereas on the touch screens they were presented with the actual line of the visual analog scale. Furthermore, whereas our study found a comparable correlation between paper and touch screen versions of this score to the validation studies[56,57], correlation is not the appropriate measure of agreement between measurement methods according to Bland and Altman[63]. Therefore, this renders some uncertainty regarding our results on the SHS score and further studies are needed.

In conclusion, with this study we found it feasible to introduce touch screens with PROs in the IBD outpatient clinic.

## 5.2. PAPER II

### 5.2.1. PRESCRIPTION PATTERNS

This population-based cohort study suggests a change in prescriptions patterns towards introducing biologics at a younger age in UC, after a shorter disease duration in CD, and in patients with less extensive disease as well as continuing biologics for a longer time in recent years.

The study has obvious strengths. It covers a long period of time, namely 16 years of real life use of IFX post-marketing. It is based on a large unselected population which is geographically well defined to the Northern part of Jutland and comprises around 583,000 citizens. There is only one center involved in collecting the data with the same core of physicians.

There are potential limitations to be mentioned. First, while Aalborg University Hospital is the only center in the region to offer biological treatment, there are other centers who refer patients to Aalborg for biological treatment. Thus, for some patients who are not cared for in Aalborg primarily, there can be a referral delay. However, this practice remains unchanged throughout the study period. Second, the distribution of missing data is unknown. Manual scrutiny of patient charts in order to retrieve information on disease extent at time of diagnosis was performed, but a substantial amount of missing data remains. Third, it is known that there has been a change in examination practice towards increased usage of magnetic resonance enterography (MRE). The study has not accounted for this. Fourth, there are no data on hospitalization.

The findings of this study are in agreement with those of other studies. Pressman and colleagues found that younger patients were more likely to initiate treatment with IFX[53]. This study was a cohort study of CD patients within a defined population. The comparison was between patients initiating IFX therapy and patients who did not. Our study included patients who initiated IFX therapy and the comparison was between time periods. Desai and colleagues showed that patients older than 60 years of age had a shorter time to discontinuation[52]. This study was a retrospective case control study of IBD patients conducted at a single referral center. Our findings that UC patients were younger at initiation of therapy, could therefore explain the longer time to discontinuation seen in regards to that study.

In conclusion, we found a change in IFX prescription patterns towards a younger age at prescription, a shorter disease duration, and a longer duration of treatment throughout the first 16 years of IFX administration in the North Denmark Region.

## 5.3. PAPER III

### 5.3.1. PREMEDICATION WITH CORTICOSTEROIDS

This cross-sectional observational study of infliximab treated Crohn's patients with or without premedication with corticosteroids was not able to find any effect of this premedication on the formation of IFX antibodies, IFX trough levels, or elimination rate of IFX regardless of concomitant AZA.

Previous studies in rheumatology have addressed this question with diverging conclusions. Focus has been on infusion reactions primarily where Choquette and colleagues found no effect of premedication[64] and Bartoli and colleagues found a relative risk of infusion reactions 2.5 times higher in a no premedication group compared to a group of patients receiving a combination of paracetamol, esomeprazole, hydrocortisone, and chlorpheniramine maleate (an antihistamine)[65].

In Gastroenterology in 2003, Farrell and colleagues performed a 16-week double-blind, placebo-controlled study of 80 consecutive patients with refractory Crohn's disease[66]. One group received 200 mg of hydrocortisone bolus and the other placebo. It was found that hydrocortisone significantly reduced antibody formation, and they suggested that premedication should be considered in some patients. However, in IBD in 2017, Gold and colleagues reported no effect of corticosteroid premedication on infusion reactions in a retrospective cohort study comprising 578 IBD patients and concluded that routine premedication use could not be recommended without future randomized control trials[67].

In our study, concomitant immunomodulator therapy with AZA was shown to reduce the formation of antibodies, and this is in accordance with previous studies[68,69].

The strengths of our study are the standardization of the blood sampling and the fact that, to our knowledge, it is the only study evaluating premedication in IFX therapy after 12-18 months of therapy in CD patients.

Potential limitations of this study are the small sample size making it possible that there was in fact an effect of premedication which was overlooked. However, we did not register even a slight tendency towards effect. Also, in this study patients were on a stable dose of IFX during at least 12 months. Thus any intolerable infusion reactions or side effects would have caused the patients to terminate the therapy earlier, making these patients not eligible to participate which might cause selection bias.

In conclusion, we were not able to detect a difference in IFX antibody formation, IFX trough levels, or IFX elimination rate in patients receiving corticosteroid premedication, leading to a change in practice in our clinic.

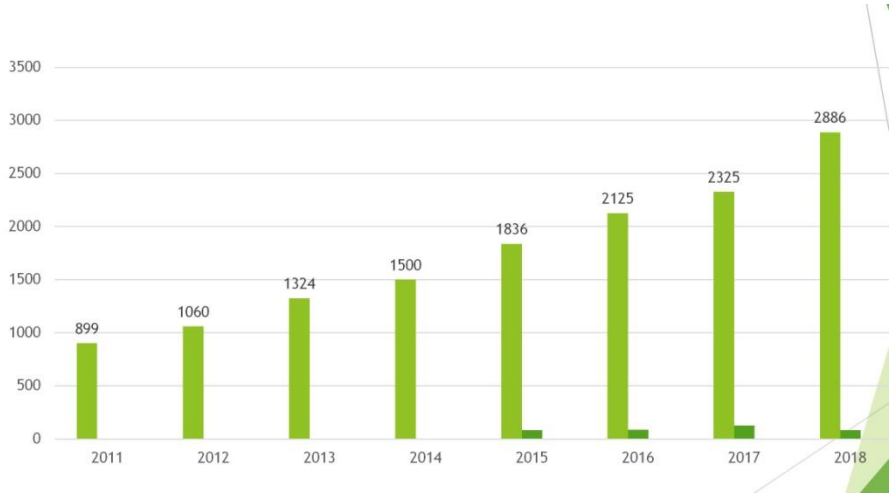
# CHAPTER 6. CONCLUSION AND CLINICAL IMPLICATIONS

The establishment of a database that serves as a tool in the clinical management of patients with IBD, has proved to enhance the management of patients due to easy, quick access to all relevant information on the individual patient with regards to their IBD diagnosis, symptoms, treatment, side effects, and procedures. This is currently not possible in the electronic patient file systems available in Denmark.

The fact that PROs are central in the structure of this database, is beneficial to the individual patient and very helpful for the physician in the clinical management of the patients' therapy. The readily accessible data on for example number of patients undergoing specific treatments makes it potentially time- and money saving for the departments as well as society.

With the studies of the present thesis, we have specifically shown that the introduction of touch screens in the outpatient clinic is feasible and it is, as mentioned, now operational in the outpatient IBD clinic at Aalborg University Hospital. Before the touch screens, only patients receiving biological treatment were given a paper questionnaire. For all other IBD patients, the physician would enquire about their symptoms, and the consistency of recording of symptoms this way was varying. Therefore, we find that data completeness has increased.

We have further provided knowledge that informs and guides our treatment with biologicals. Changes towards younger age at prescription of biologic drugs and a longer treatment period are challenging a health care system, where resources are scarce. Every year there is an increasing number of patients being treated with biologics at the IBD outpatient clinic in Aalborg (Figure 6-1). This has recently been illustrated as part of budget negotiations.




*6-1 Number of biological infusions in Aalborg by year*

Lastly, our studies have changed clinical practice, when it comes to premedication with corticosteroids. The lack of effect on corticosteroid premedication in IFX treatment of patients with Crohn's disease has led to termination of premedication at the IBD outpatient clinic at Aalborg University Hospital.

All in all, this thesis illustrates that it is feasible to establish a database for IBD patients serving a number of purposes. This database now guides clinical practice, routinely delivers data to the mandatory national quality registry, it serves as a source for research, for recruitment of patients for research, and as a research cohort for observational studies.

# CHAPTER 7. FUTURE PERSPECTIVES

The database and related touch screens have enhanced our treatment of patients. In particular, the extended use of PROs may qualify treatment in the future. Further development of algorithms for managing patients from home is already ongoing. Regular transmission of activity scores to GASTROBIO via an online platform may ideally render annual consultations superfluous in the future and enable "on-demand" consultations. This is both a meaningful use of resources and also more patient friendly, as patients no longer have to take time off work to consult with their IBD physician at random times. Patients are now able to log on from their home personal computer with a link supplied by the clinic. This feature has been tested, but is currently not in use. Also development of an app for mobile phones is ongoing.

The establishment of GASTROBIO has provided the IBD team at Aalborg University Hospital with a unique ability to perform research. At any given time point, there is a complete knowledge of the number of patients in the North Denmark Region receiving biological treatment enabling us to perform multiple studies both in our own clinic, but also in collaboration with other clinics and universities.

Other gastroenterology databases exist in Denmark, but none contain information in this detail on patient level and cover such a large geographical area, and hence the data are unique. However, the data in this database can be migrated to other databases, if consensus is reached in Denmark or even in Europe, on using the same platform everywhere. Furthermore, it is also possible to combine detailed information on the approximately 6,600 IBD patients diagnosed during 1978-2016 with information from the Danish National Hospital Registry (LPR), thereby enabling the study of a wide range of long-term outcomes among IBD patients as compared to the general population. When such studies are normally conducted by use only of the national registries, individual level information on smoking habits and phenotypic characteristics are lacking.

Hence, with the great advantage of detailed patient characteristics in the present cohort, we plan to conduct a number of future studies on

- the development of primary sclerosing cholangitis and cancer in IBD patients. Are there phenotypic similarities in these patients?
- the mortality/morbidity in IBD patients in relation to medical therapy, age, disease activity, compared to the healthy population

- the prognosis of IBD patients receiving biological therapy compared with IBD patients receiving standard therapy in regards to symptoms, fistulas, surgery, mortality

In collaboration with others, we are planning the following studies:

- The Danish IBD biobank (DIB): Predictors of treatment response and disease course in patients with inflammatory bowel disease treated with biological therapy. Collaboration with Hvidovre, Herlev, Aarhus.
- ISCAN: Inflammatory Bowel Disease - Scandinavian cancer in IBD study. Collaboration with Oslo, Norway, and Sweden.
- Extra Intestinal Manifestations in IBD. Collaboration with Department of Infectious Diseases, Aalborg University Hospital and Division of Gastroenterology, Department of Medicine, University of California, San Francisco.
- Stem cells for fistulas - Aarhus University Hospital in collaboration with multiple Danish centers.

Overall, the possibilities are numerous when data are being collected prospectively and real-time as is the case with GASTROBIO.

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# APPENDIX: PAPERS I, II, III

# Paper I: Touch screens as a tool in patient care in the IBD outpatient clinic

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# Touch screens as a tool in patient care in the IBD outpatient clinic

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**ABSTRACT**

**Objective:** We have introduced online touch screens in the waiting room for patients with ulcerative colitis (UC) or Crohn's disease (CD) for recording of symptoms before their consultation. This has made disease activity scores readily available to the physician in our newly established database, 'Gastrobio'. We wanted to validate the use of touch screens compared to paper questionnaires.

**Material and methods:** A total of 54 patients with UC and 74 patients with CD were included in the study. The UC patients filled out the Short Health Scale (SHS) and Simple Clinical Colitis Activity Index (SSCAI). The CD patients filled out the SHS and Harvey–Bradshaw Index (HBI). Paper questionnaires and touch screen versions were used in random order and comparison between the two modalities was made by Spearman correlation test, Bland–Altman plots, and Kappa-statistics.

**Results:** Among the 128 patients, the two SHS scores (SHS touch versus SHS paper) were found to be highly correlated (Spearman correlation; 0.92 for UC and 0.92 for CD). Also, on average, Bland–Altman plots demonstrated a difference close to zero between the two modalities. Agreement between paper version and touch screen version of SCCAI and HBI scores was also high (Kappa-statistics; 78% raw and 98% weighted for SCCAI; 65% raw and 97% weighted for HBI).

**Conclusions:** It is feasible to introduce touch screens in the outpatient clinic and to have patients record their symptoms before the consultation. However, the study may not be representative for elderly patients.

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## Introduction

The two inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's disease (CD), are primarily managed in outpatient clinics. Symptoms of the diseases are reported by the patients and form a substantial part of the assessment of disease activity and the effect of treatment. At the Department of Gastroenterology and Hepatology at Aalborg University Hospital, we have introduced online questionnaires on touch screens in the waiting room instead of paper versions or oral interview by the physician. This approach has previously been shown to be feasible in other diseases with different questionnaires.[1–7] The introduction of the touch screens in our clinic is part of the establishment of a database, 'Gastrobio', which comprises clinical information on more than 5000 IBD patients from the North Denmark Region. It is a web-based solution based on open-source software.

A previous study has validated the use of touch screens in the Danish nationwide rheumatology registry, DANBIO, showing that the introduction of touch screens is feasible.[1] DANBIO includes patients with rheumatoid arthritis (RA), psoriasis arthritis (PsA), and ankylosing spondylitis (AS) and was initiated in the year 2000. Since 2005, an online web-based version of the database based on the use of touch screens has been available.[8] Every rheumatology outpatient clinic in Denmark uses this system, but the scores are of course different from IBD scores. The use of touch screens in evaluation of IBD patients has not been validated in Denmark.

Relevant scores in IBD patients are the Short Health Scale (SHS), the Simple Clinical Colitis Activity Index (SCCAI), and the Harvey–Bradshaw Index (HBI). The SHS is a score to evaluate health related quality of life. SCCAI and HBI are simple and obtainable disease specific scores without laboratory results and diary information.[9,10] Using these scores, we found it feasible to introduce touch screens for our patients. We assumed that patients would be less likely to omit answers on touch screens than on a paper version of the questionnaires, but we also had the concerns that the elderly might have trouble with the touch screens.

We hypothesized that there would be no difference between answers to paper questionnaires and answers to touch screen questions. Our aim was to compare the two modalities and to evaluate differences in 1) SHS and SCCAI scores among UC patients, 2) SHS and HBI scores among CD patients, and 3) number of missing answers using the two approaches.

## Methods

### *Patients*

Between 21 August 2015 and 18 September 2015, we asked 57 UC patients and 75 CD patients to participate in the present study. Patients came to the outpatient clinic at the Department of Gastroenterology, Aalborg University Hospital

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for a scheduled consultation with a physician or for the administration of a biological agent. Three UC patients and one CD patient were excluded due to error in procedure (by mistake, UC patients were given the CD questionnaire and the CD patient was given the UC questionnaire).

A total of 54 UC patients and 74 CD patients were included in the study. We planned to ask half of the patients to fill out the paper questionnaire first. However, some patients reached the touch screen before we could approach them, why the number of patients using the touch screen first was 85, whereas 43 answered the paper questionnaire first. Immediately after, patients were asked to answer the questionnaire again using the different tool, and, thereby, all patients completed both paper and touch screen questionnaires.

### Questionnaires

All patients received questions on weight, smoking habits, and adverse events. In addition, the UC patients filled in the SHS and SCCAI questions and the CD patients filled in the SHS and HBI questions.

The SHS is a visual analog scale, but the paper version in our clinic demands a score between zero and 100. The SCCAI and HBI items are answered by checking off boxes either on paper or on the touch screen.

The paper questionnaires were self-administered as were the touch screens. The patients only received help from the staff upon request. The paper questionnaires were handed out to the patients upon arrival to the clinic either from the nurse, doctor, or secretary, and they were asked to approach the touch screen to enter their symptoms.

The data collected on paper was manually processed and entered into the statistical program Stata/IC 12.1 for Windows (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP) The data collected on the touch screens were immediately processed and available in the Gastrobio database. These data were transferred into Stata for statistical analysis.

Patients who had omitted a specific answer either on paper or on touch screen were excluded only for that particular score when performing subsequent comparison of answers. Some patients were excluded for a particular subscore as it was clear from the charts that they had misunderstood the question on paper.

### Statistical analysis

The average of the four SHS subscores was calculated for both the paper and the touch versions and the difference (paper version minus touch version) was calculated. The same was done for the SHS subscores. The SCCAI and HBI scores were compared subscore by subscore.

In order to be able to compare our results with previous studies on SHS scores, the Spearman correlation coefficient was calculated for these scores.[11,12] Further visualization was done by Bland–Altman plots.

For the SCCAI and HBI scores, the Kappa-statistic measure of agreement was performed on both raw (no acknowledgement of the importance of disagreements) and weighted (defined weights of importance of disagreements, a disagreement of one point was weighted lower than a disagreement of three points).

To test for differences in missing data patterns, McNemar's exact significance test was performed.

### Ethical statement

All patients agreed to participate. According to Danish law, the study did not require approval from the Regional Ethics committee.

## Results

The 54 included UC patients had a mean age of 43 years (range 19–74 years) and 52% were males. The 74 included CD patients had a mean age of 39 years (range 14–78 years) with 47% being males. All 128 patients filled out both the paper and touch screen questionnaire in random order and Table 1 summarizes the characteristics for the two groups.

### The Short Health Scale

A total of 46 UC patients (85%) and 59 CD patients (80%) had complete SHS scores. The two scores (SHS touch versus SHS paper) were highly correlated (Spearman correlation; 0.92 for UC and 0.92 for CD). On average, Bland–Altman plots (Figure 1) demonstrated no difference (mean difference 1.23 for UC and −0.85 for CD).

Some patients (three UC and five CD) had clearly mistaken the SHS scale on paper especially regarding the general well-being where they mistook good for bad and vice versa. They would typically score zero on the touch screen for all four subscores and 100 on paper for one subscore and zero for the other three.

### The SCCAI and HBI

The SCCAI and HBI scores were evaluated by means of the Kappa-statistic measure of agreement, which was high (SCCAI: 78% raw, 98% weighted; HBI: 65% raw, 97% weighted) suggesting that patients would give the same score on paper and touch screen.

### Missing data

Missing data was more prevailing in paper versions than touch versions (Table 2), however, none of the differences proved to

**Table 1.** Characteristics of patients with inflammatory bowel disease participating in the validation of touch screens vs. paper questionnaires.

| | UC | CD |
|---|---|---|
| *N* | 54 (100%) | 74 (100%) |
| Gender males | 28 (52%) | 35 (47%) |
| Gender females | 26 (48%) | 39 (53%) |
| Age, mean (min/max) | 43 (19/74) | 39 (18/78) |
| Age >65 | 5 (9%) | 2 (3%) |
| Smokers | 9 (17%) | 13 (18%) |
| Non-smokers | 45 (83%) | 61 (82%) |
| Stomi Yes | | 8 (10%) |
| Stomi No | | 66 (90%) |
| Sequence | | |
| Touch screen first | 33 (61%) | 52 (70%) |

UC: ulcerative colitis; CD: Crohn's disease.

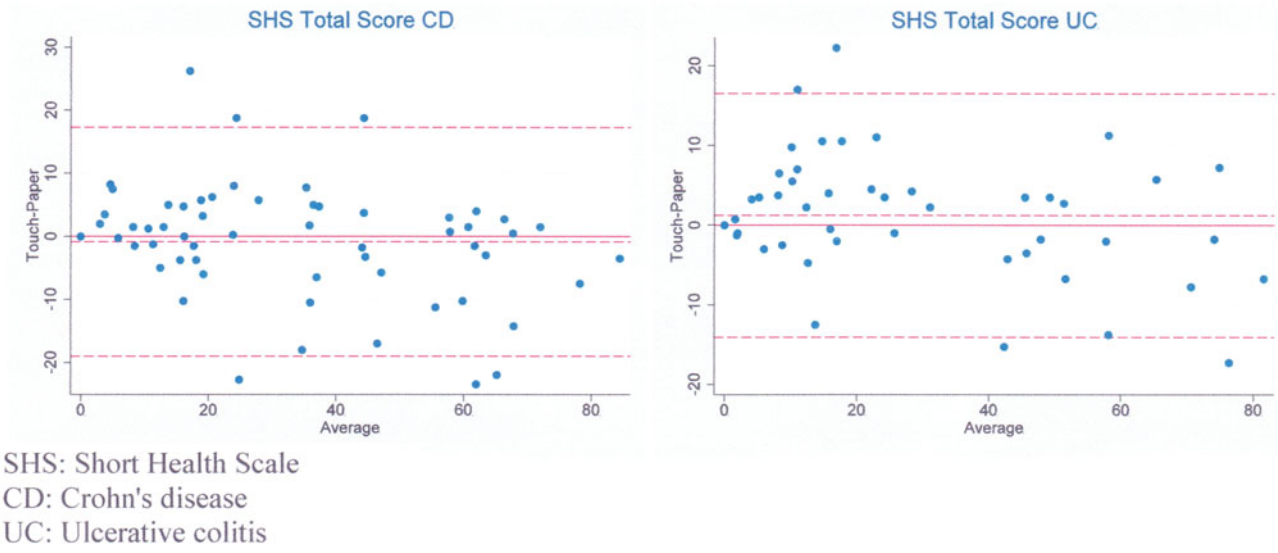


**Figure 1.** Bland–Altman plots of SHS for UC and CD. The full-drawn line marks the zero value on the ordinate. The dotted horizontal lines mark the mean difference and the limits of agreement, which are defined as the mean difference plus and minus 1.96 times the standard deviation of the differences.

**Table 2.** Distribution of complete answers and scores.

| | UC | | | | CD | | | |
|---|---|---|---|---|---|---|---|---|
| | Touch | | Paper | | Touch | | Paper | |
| | *N* | Score Mean (Std) | *N* | Score Mean (Std) | *N* | Score Mean (Std) | *N* | Score Mean (Std) |
| All | 54 | | 54 | | 74 | | 74 | |
| SHS total | 53 | 29.3 (23.7) | 46 | 30.1 (26.0) | 71 | 35.0 (23.6) | 65 | 34.4 (24.5) |
| SHS symptoms | 54 | 28.6 (25.9) | 51 | 28.1 (27.5) | 72 | 32.9 (25.9) | 72 | 32.5 (27.1) |
| SHS activity | 53 | 25.5 (28.3) | 53 | 25.5 (30.6) | 71 | 32.6 (27.6) | 69 | 31.1 (28.5) |
| SHS worry | 54 | 34.8 (26.1) | 51 | 36.0 (29.2) | 74 | 38.0 (27.2) | 71 | 38.2 (28.4) |
| SHS well-being | 54 | 28.1 (23.5) | 51 | 30.5 (31.4) | 72 | 35.2 (25.2) | 68 | 37.8 (29.9) |
| SCCAI (total) | 54 | 2.9 (3.0) | 51 | 2.7 (2.9) | | | | |
| Bowel frequency day | 54 | 0.2 (0.7) | 53 | 0.3 (0.7) | | | | |
| Bowel frequency night | 54 | 0.2 (0.4) | 53 | 0.2 (0.4) | | | | |
| Urgency of defecation | 54 | 0.7 (0.8) | 54 | 0.6 (0.7) | | | | |
| Blood in stool | 54 | 0.7 (1.0) | 53 | 0.5 (0.8) | | | | |
| General well-being | 54 | 0.6 (0.7) | 54 | 0.6 (0.8) | | | | |
| Extra-colonic features | 54 | 0.5 (0.6) | 54 | 0.5 (0.6) | | | | |
| HBI (total) | | | | | 64 | 5.2 (4.2) | 62 | 5.2 (4.4) |
| General well-being | | | | | 74 | 0.9 (0.8) | 74 | 0.8 (0.8) |
| Abdominal pain | | | | | 73 | 0.9 (1.0) | 72 | 0.7 (0.9) |
| Number of liquid stools/day | | | | | 67 | 2.1 (2.7) | 64 | 2.3 (3.4) |
| Abdominal mass | | | | | 74 | 0.3 (0.7) | 68 | 0.3 (0.8) |
| Complications | | | | | 73 | 1.0 (1.0) | 71 | 1.0 (1.0) |

UC: ulcerative colitis; CD: Crohn's disease; Std: standard deviation; SHS: Short Health Scale; SCCAI: Simple Clinical Colitis Activity Index; HBI: Harvey–Bradshaw Index.

be statistically significant. Only five (9%) UC patients and two (3%) CD patients were over 65 years of age, and therefore analyses of distribution of missing answers among the elderly could not be performed. Of the five UC patients, one 74-year old patient had misunderstood the SHS well-being score and had to be excluded for this subscore, and another patient (65 years old) had omitted subscores for the SCCAI and had to be excluded for this score. The two CD patients (67 and 78 years of age) had both omitted answers in two SHS subscores and were excluded from evaluation of these scores.

## Discussion

In this validation study of self-reporting of symptoms and well-being among 128 IBD patients, we observed that touch screens in the waiting room provided a valid method for data collection as compared with paper questionnaires.

In our clinic, we have now had more than 1000 patient visits since the touch screens were introduced, and we have not experienced any major problems in using them. Our touch screens provide immediate accessibility to the answers for the physician and this ensures complete recording of patient related data at every visit since data collection is no longer dependent on the doctor or nurse remembering to ask all the questions. Furthermore, the delay related to processing of paper questionnaires is avoided. The present study confirms the validity of the touch screen approach as compared to former questionnaire methods. In rheumatology, similar experiences have been made.[1]

The theory that familiarity makes a difference was supported by the satisfactorily concordant HBI and SCCAI scores, which are more familiar to the IBD patients in our clinic than the SHS scores. This analysis has not been done previously in other studies.

The present study had strengths and limitations that need to be considered. A strength of this study is that the patients were familiar with SCCAI and HBI questions, as these scores have been used in our clinic for many years. Therefore, differences in answers between paper questionnaires and touch screens were not confounded by difficulties in understanding the questions.

The touch screen demands an answer, and while it is possible to proceed without answering, this can only happen after actively accepting to omit the answer. Probably for this reason, the number of missing data was higher in the paper group and although not statistically significantly so, this favors the use of touch screens. We saw examples of UC patients receiving CD questionnaires and vice versa (in totally four patients) on the paper version due to a mistake while handing out the paper questionnaire. This did not occur with the touch screens as the system automatically provides the questionnaires based on the registered diagnosis of the patient.

A potential limitation of the present study is the short time elapsed between answering questions on the touch screen and paper version. The former study of touch screens in rheumatology used the same approach, whereas Hjortwang et al. and Stjernman et al. validated the SHS score by retesting after two and four weeks, respectively.[11,12] However, the usefulness of the latter approach in patients with IBD is questionable, as symptoms may change over weeks, which would result in true changes in scores and not reflect differences in use of touch screens and paper questionnaires.

Also, we only used the validated visual analog scale of 100 mm on touch screens, not in paper questionnaires, because this scale had not been implemented on the paper version in our clinic. Therefore, the validity of the results regarding the SHS scores can be questioned. Our IBD patients are not used to the score, which could have influenced results and we have to consider the possibility that this score is not fully understood by patients.

Another potential limitation was the use of the HBI subscore 'Abdominal mass', which we let the patient evaluate without examination by a doctor. This is of course not the optimal use of this score. Also, the HBI score is validated for patients without previous abdominal surgery, and we used it for all CD patients including patients with a stoma. However, this is not likely to affect the result, since we only compared methods of registering within the same patient.

It may be assumed that elderly patients would find the touch screens difficult to operate, but we did not include enough patients above 65 years to investigate this assumption. Nurses and doctors reported that especially the elderly needed assistance the first time. This was not the case for younger patients. In our study, we saw omission of answers or misunderstandings in more than half of the elderly participants. Further studies with age stratification are needed to evaluate this hypothesis.

Regarding the SHS score, we found that the correlation between the touch screen version and paper version was comparable to previous validation studies of the SHS.[11,12] However, it is well known that correlation is not an appropriate measure of agreement between measurement methods.[13]

We therefore used the Bland–Altman plots to illustrate the agreement between the two methods (touch screen and paper questionnaire). As the data can only attain values from zero to 100, small averages will always be accompanied by small differences and therefore the plots will exhibit some degree of funnel shapeness for this data. The Bland–Altman plots suggested some randomness in the answers with wide limits of agreement for the SHS score. As a clinician, attention needs to be directed to this fact when using the SHS score.

In conclusion, we found that the introduction of touch screens instead of paper questionnaires is feasible in the IBD outpatient clinic. Instructions are normally not needed, but attention may be directed to the elderly, who in our experience need assistance.

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## Disclosure statement

The authors have nothing to disclose and no conflicts of interest exist.

## Funding information

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# Paper II: Changing Infliximab Prescription Patterns in Inflammatory Bowel Disease: A Population-Based Cohort Study 1999-2014

# Changing Infliximab Prescription Patterns in Inflammatory Bowel Disease: A Population-Based Cohort Study, 1999–2014

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**Background:** Long-term data on real life use of infliximab (IFX) for inflammatory bowel disease (IBD) are lacking. We studied prescription patterns during the first 16 years following marketing authorization.

**Methods:** In a population-based cohort from the North Denmark Region, all IBD patients exposed to IFX during 1999 to 2014 were identified.

**Results:** A total of 623 patients (210 with ulcerative colitis [UC] and 413 with Crohn's disease [CD]) were exposed to IFX. In patients with UC, age at first exposure decreased by 10 months per calendar year ($P < 0.05$) during the study period. In patients with CD, disease duration at time of first IFX exposure decreased by 7 months per calendar year ($P < 0.001$). From 2005–2009 to 2010–2014, the proportion of IFX-exposed patients with pancolitis (40% vs 24%, $P = 0.04$) and the proportion of patients with extensive CD ($P = 0.002$) decreased. The mean time to discontinuation of IFX remained stable in patients with CD during the study period (2.5–3.0 years) and increased from 0.34 years (2005–2009) to 1.11 years (2010–2015) in patients with UC ($P = 0.04$).

**Conclusion:** During the first 16 years postmarketing, age at first exposure to IFX decreased in patients with UC, whereas disease duration at time of first exposure decreased in patients with CD. Also, a significant change toward less extensive disease in both UC and CD patients exposed to IFX was observed. Treatment duration in patients with UC increased during the study period, but did not reach the more constant and longer duration of treatment observed in patients with CD.

**Key Words:** indications, inflammatory bowel disease, infliximab, prescription patterns

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory bowel diseases (IBDs) mainly affecting the gastrointestinal tract. Patients are often diagnosed in young adulthood, and treatment has conventionally included topical and oral 5-aminosalicylates and corticosteroids, surgery, and, in more recent decades, also thiopurines and other immunosuppressants. Immunotherapy with biological agents was introduced by the end of the last millennium and has been used increasingly for treatment of IBD since then.[1–6]

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As the first biological agent, infliximab (IFX) was approved in 1998 for treatment of CD and in 2005 for UC. Knowledge of the use of IFX for IBD primarily comes from clinical trials. Few studies are based on observational data, and their main focus is safety of IFX.[7–21] These studies have demonstrated that IFX is effective and safe. Additional studies have indicated that IFX may improve prognosis of the disease with decreasing surgery rates.[22]

Few studies describe the patient population exposed to IFX in real life. Two studies suggest that IBD patients starting IFX therapy are younger than patients treated with conventional therapy,[23, 24] but this may have changed with the gradually increasing use of IFX since its introduction to the market. The increasing use of IFX may also reflect treatment of a broader spectrum of patients with less extensive disease or treatment of the individual patient for a longer period of time.

We aimed to elucidate these hypotheses by assessing real-life use of IFX in a population-based IBD cohort followed from 1999 to 2014 in order to describe changes in prescription patterns with a focus on temporal changes in patient characteristics, treatment indications, and treatment duration.

## MATERIALS AND METHODS

### Study Population

We conducted a population-based cohort study of all IBD patients treated with IFX between 1999 and 2014 in the North

Denmark Region (583,000 inhabitants). Patients were identified through GASTROBIO, a web-based registry of IBD patients established both for research purposes and to optimize clinical management.[25] All patients with a diagnosis of UC or CD who had been treated with IFX as their first biologic agent during 1999–2014 were included. The initial dosing of IFX was 5 mg/kg at weeks 0, 2, and 6, and then every 8 weeks. Hereafter the interval could vary from 6 to 10 weeks and the dose from 5 mg/kg to occasionally 10 mg/kg. No patients were on intermittent IFX dosing.

IFX has been administered to CD patients since 1999 and to UC patients since 2005 at Aalborg University Hospital as the only place in the North Denmark Region to offer biological therapy. This hospital is a primary center for the population living around the city of Aalborg, but a secondary center for patients living farther away who would require referral for evaluation and commencement of IFX. The region has a tradition for collecting data on all IBD patients dating back to 1978[26] and has since the introduction of IFX recorded all patient characteristics and treatments in the GASTROBIO database.[25] GASTROBIO delivers data to the Danish National Registry for Biological Therapy in Inflammatory Bowel Disease (BIO-IBD). Entering data into BIO-IBD is mandatory in all departments in Denmark prescribing biological therapy.[27]

## Definitions

### *Indications*

Indications for treatment were entered by the treating physician into GASTROBIO and covered the following categories: "acute severe UC," "chronically active UC," "luminal CD," and "fistulizing CD." We defined "acute severe UC" according to Danish national guidelines, which are in accordance with the ECCO guidelines.[28, 29]

### *Disease extent*

Disease extent was determined based on endoscopic and radiological findings. For UC patients, disease location was divided into 2 groups: leftsided and pancolitis. According to the Montreal classification, upper gastrointestinal disease was used as a modifier for the rest of the locations (ileal, ileocolonic, and colonic disease) for CD.[30]

## Statistical Analyses

We used mean and standard deviation for descriptive statistics of continuous variables and provided total numbers and percentages for the categorical variables.

For all statistical analyses, 2-sided tests were applied with corresponding *P* values, using a significance level of 5%.

To assess changes over time, linear regression was performed on age at exposure and disease duration by year of first IFX exposure, and results were presented as a slope with 95% confidence intervals (CIs). A *P* value for the test of 0 slope was also presented. To evaluate early user bias, we conducted sensitivity analyses removing the years 1999–2003. This did not apply to UC patients in whom IFX was first used from year 2005, when clinicians were experienced in using the drug for CD. For the categorical variables "indications" and "disease extent," we assessed temporal changes by comparing the 2 time periods 2005–2009 and 2010–2014 for UC and 1999–2009 and 2010–2014 for CD using the $\chi^2$ test.

Likewise, time to discontinuation was analyzed using Kaplan-Meier curves, and the differences between the periods 2005–2009 and 2010–2014 for UC and 1999–2009 and 2010–2014 for CD were compared using the log rank test. In order to further qualify the time to discontinuation analyses, we performed Cox regression analysis. Results were expressed as hazard ratios (HRs) with 95% CIs.

Analyses were performed using Stata (Stata/IC 12.1 for Windows, www.stata.com).

# ETHICAL CONSIDERATIONS

The study was approved by the Danish Board of Health (3-3013-720/1) and the Danish Data Protection Agency (2008-58-0028).

# RESULTS

## Patient Characteristics

From 1999 to 2014, 717 IBD patients received biological therapy. Of these, 94 patients (13.1%) were excluded: 8 (1.1%) due to a diagnosis of "IBD unclassified," 2 (0.3%) did not have IBD, 37 (5.2%) were treated with a different biological agent as their first biological treatment, and 47 (6.6%) had started treatment at a hospital outside the region. This left 623 patients (210 with UC and 413 with CD) exposed to IFX as their first biological agent available for analyses. Ninety-five (15%) of these patients (33 UC and 62 CD) were referred from a different hospital in the region for biological treatment. Of these, 35 patients (5 UC and 30 CD) were referred during years 1999–2009, and 60 patients (28 UC and 32 CD) during the years 2010–2014. Baseline characteristics are shown in Table 1. Age distribution at time of diagnosis is shown in Fig. 1.

## Patient Age and Disease Duration

### *Age at exposure*

Overall, the mean age at first exposure to IFX was 37.0 years for UC patients and 34.5 years for CD patients. During years 2005–2014, the age at first IFX exposure decreased by approximately 10 months or 0.8 years per calendar year (95% CI, –1.58 to –0.03; $P < 0.05$) in patients with UC. In the overall period (1999–2014), age at first exposure to IFX in patients with CD did not change significantly (–0.12 years/calendar year; 95% CI, –0.49 to 0.26; $P = 0.53$). The sensitivity analysis for CD (2004–2014 only) was insignificant as well (–0.17 years/calendar year; 95% CI, –0.67 to 0.34; $P = 0.52$).

**TABLE 1. Baseline Characteristics of a Population-Based Cohort of Patients With Inflammatory Bowel Disease Exposed to Infliximab (1999–2014)**

| | Ulcerative Colitis | Crohn's Disease | Total |
|---|---|---|---|
| Patients, No. (%) | 210 | 413 | 623 |
| Male | 108 (51) | 170 (41) | 278 (45) |
| Female | 102 (49) | 243 (59) | 345 (55) |
| Age at diagnosis, No. (%) | 210 | 413 | 623 |
| Mean (SD), y | 30.5 (14.9) | 28.1 (12.9) | 28.9 (13.6) |
| Age at IFX, No. (%) | 209 | 412 | 621 |
| Mean (SD), y | 37.0 (15.8) | 34.5 (14.3) | 35.4 (14.8) |
| BMI, No. (%) | 150 | 315 | 465 |
| Mean (SD), kg/m$^2$ | 25.9 (5.5) | 24.3 (5.4) | 24.8 (5.5) |
| Smoker, No. (%) | 207 | 397 | 604 |
| Yes | 20 (9.7) | 141 (35.5) | 161 (26.7) |
| Previous | 65 (31.4) | 80 (20.2) | 145 (24.0) |
| Never | 104 (50.2) | 160 (40.3) | 264 (43.7) |
| Unknown | 18 (8.7) | 16 (4.0) | 34 (5.6) |
| IBD family history, No. (%) | 181 | 372 | 553 |
| Yes | 28 (15.5) | 64 (17.2) | 92 (16.6) |
| No | 153 (84.5) | 308 (82.8) | 461 (83.4) |
| Indication for IFX, No. (%) | 182 | 257 | 439 |
| Severe acute UC | 58 (31.9) | | |
| Chronically active UC | 124 (68.1) | | |
| Fistulizing CD | | 58 (22.6) | |
| Luminal CD | | 199 (77.4) | |

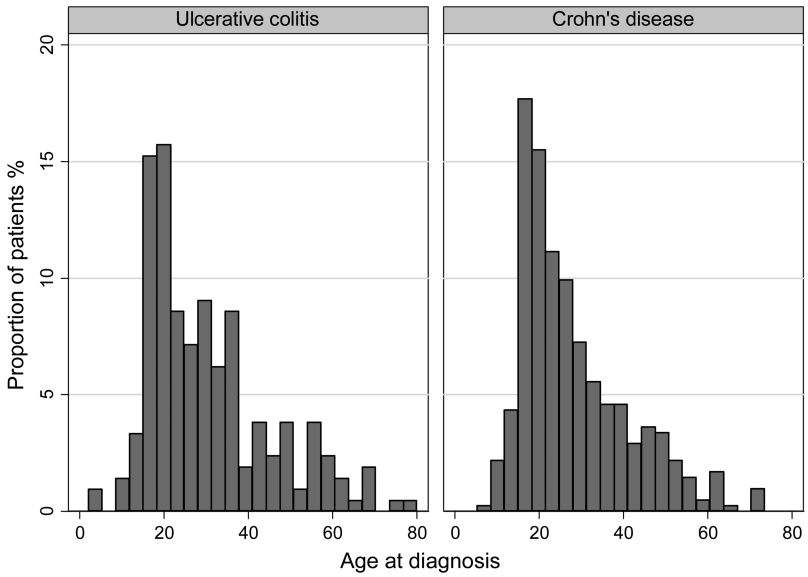


FIGURE 1. Age distribution at time of diagnosis in patients with inflammatory bowel disease later treated with infliximab.

## *Disease duration*

Overall, the mean time from IBD diagnosis to first IFX exposure was 6.5 years in both UC and CD patients and 6.0 years in CD patients when analyzing years 2004–2014 only. Time to first IFX exposure did not change during the study period among patients with UC (reduction of 0.26 years/calendar year; 95% CI, –0.78 to 0.26; $P$ = 0.30), while in patients with CD, a decrease in time to first exposure of approximately

7 months or 0.6 years per calendar year (95% CI, –0.84% to –0.33%; $P < 0.001$) was observed. This was also the case when studying years 2004–2014 only (a decrease of approximately 5 months or 0.41 years per calendar year; 95% CI, –0.72% to –0.01%; $P < 0.03$).

## Indications

The indication for starting treatment with IFX was known for 93% of UC patients. Of these, 32% had severe acute UC and 68% had chronically active UC. The indication was known for 62% of CD patients, with 23% having fistulizing disease and 77% having luminal disease. Although the absolute number of patients receiving IFX during the period increased, the distribution of indications did not change significantly from before 2010 to 2010–2014, when comparing proportions of severe acute and chronically active disease in UC (32% vs 68% in both periods, $P = 1.00$) and fistulizing and luminal disease in CD (21% and 79% before 2010 vs 24% and 76% in 2010–2014, $P = 0.66$).

## Disease Extent

Data on disease extent were available for 149 (71%) of UC patients and 284 (67%) of CD patients. Disease extent at diagnosis in patients exposed to IFX in the first vs the second calendar period is shown in Fig. 2 for UC and in Fig. 3 for CD. The proportion of UC patients with pancolitis was higher in the group initiating IFX treatment between 2005 and 2009 (40%) than in patients initiating treatment between 2010 and 2014 (24%) ($P = 0.04$) (Fig. 3). In the latter period, patients were more likely to have left-sided colitis. In patients with CD, we observed an increase in the proportion of patients with isolated ileal disease exposed to IFX from the period 2005–2009 (4%) to the period 2010–2014 (13%), while the proportion of patients with more extensive disease decreased ($P = 0.006$) (Fig. 3).

## Duration of Treatment

In patients with UC, the median interval from start of treatment with IFX to discontinuation increased significantly from 0.34 years in patients exposed to IFX during 2005–2009 to 1.11 years in patients starting treatment during 2010–2014, as reflected by an HR of 1.42 (95% CI, 1.02 to 1.98; $P = 0.04$) (Fig. 4).

In patients with CD, the median duration of IFX treatment was almost 3 years in both 2005–2009 (2.57 years) and 2010–2014 (2.96 years), and, accordingly, our regression analysis showed an HR of 0.93 (95% CI, 0.71 to 1.22; $P = 0.60$) (Fig. 5).

Causes for discontinuation are shown in Table 2. Remission was the cause for discontinuation in slightly more UC (41.8%) than CD (31.8%) patients ($P = 0.05$). This was also the case for poor response (35.3% in UC vs 23.4% in CD, $P = 0.01$). Adverse events were an almost equally common course in UC

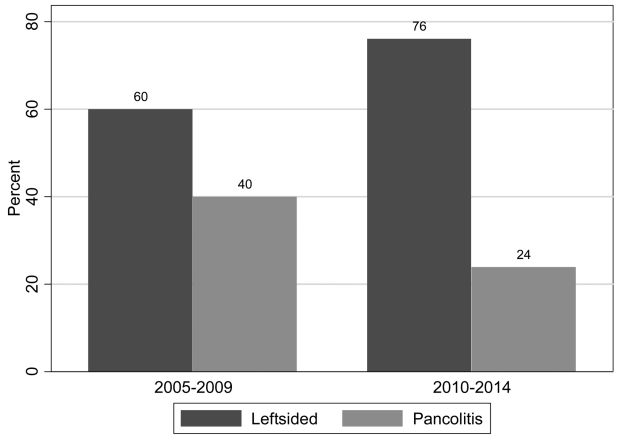


FIGURE 2. Disease extent at time of diagnosis of ulcerative colitis by period of first infliximab prescription (n = 147).

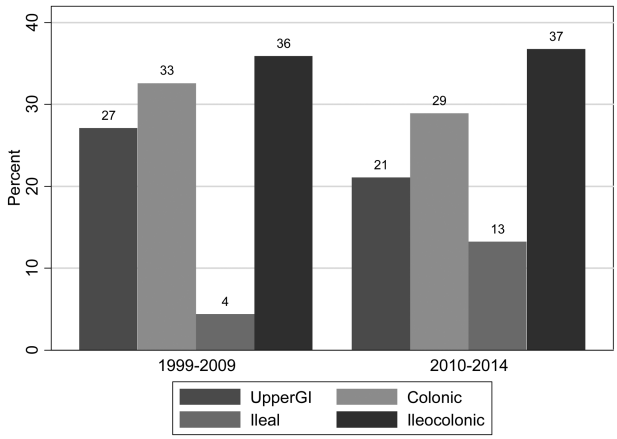


FIGURE 3. Disease extent at time of diagnosis of Crohn's disease by period of first infliximab prescription (n = 284).

patients (5.2%) and CD patients (11.3%, $P = 0.07$), whereas surgery was the cause in only 6.7% of CD patients vs 19.6% of UC patients ($P < 0.001$).

## DISCUSSION

In the present population-based cohort study, we describe real-life use of IFX in a geographically well-defined IBD population observed from the beginning of the biological era and 16 years ahead. Our data revealed that IFX was introduced at an increasingly younger age in UC during the observation period and that the interval from diagnosis to IFX exposure became shorter in CD. Further, the proportion of patients treated for extensive disease decreased during the period in both CD and UC, whereas indications (acute vs chronic disease in UC and fistulizing vs luminal in CD) did not change over time. Of note, time to discontinuation of treatment remained stable in patients with CD during the study period, but it increased in patients with UC, without reaching the level observed in patients with CD, however.

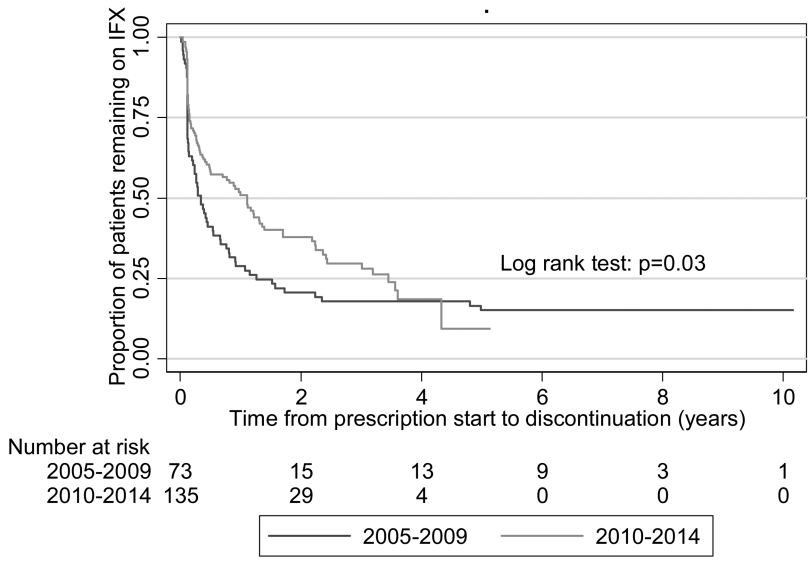


FIGURE 4. Time from first infliximab prescription to discontinuation in a population-based cohort of patients with ulcerative colitis (n = 208).

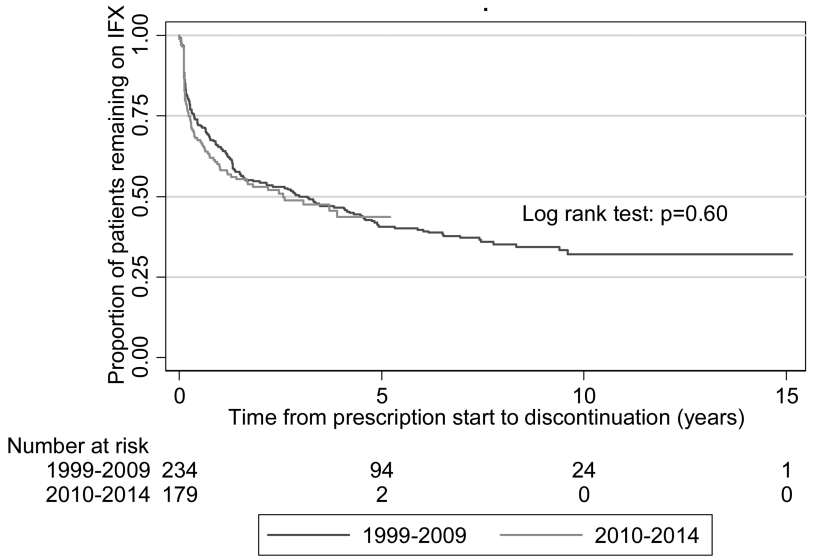


FIGURE 5. Time from first infliximab prescription to discontinuation in a population-based cohort of patients with Crohn's disease (n = 413).

The present study has several strengths. First, data were collected in 1 center with the same core of physicians throughout the period. Second, the population is geographically well defined and covers 583,000 citizens, which allows the study of the real-life use of the first available biological agent, IFX, in an unselected population during the first 16 years postmarketing. This is an incomparably long study period. Third, our study reflects the daily life of a large outpatient clinic offering biological therapy. Representing a real-life setting, which is less controlled than phase 3 drug testing, our population enables the study of the true and broad spectrum of patients with no selection related to age, previous surgery, or other common exclusion criteria.

The study also has potential limitations, which need to be considered. First, while Aalborg University Hospital is a primary center for the part of the population in the North Denmark Region centered on the city of Aalborg, it is also a secondary center for patients living farther away in the region. These patients have a different primary center that does not offer biological therapy, and therefore, there could be a delay in referring these patients to treatment. This could not be taken into account in the present study, but it hardly affects results, as there has been no change in the organization of health care during the study period. Second, there is no knowledge on how the missing data are distributed in this study. Initially, GASTROBIO did not register disease extent

**TABLE 2. Causes for Discontinuation of Infliximab Treatment in a Population-Based Cohort of Patients With Inflammatory Bowel Disease (1999–2014)**

| | Ulcerative Colitis No. (%) | Crohn's Disease No. (%) | *P* | Total No. (%) |
|---|---|---|---|---|
| No. (%) | 153 (100) | 239 (100) | | 392 (100) |
| Remission | 64 (41.8) | 76 (31.8) | 0.05 | 140 (35.7) |
| Poor response | 54 (35.3) | 56 (23.4) | 0.01 | 110 (28.1) |
| Adverse events | 8 (5.2) | 27 (11.3) | 0.07 | 25 (6.4) |
| Cancer | 0 (0.0) | 1 (0.4) | 1.00 | 1 (0.3) |
| Change of hospital | 1 (0.7) | 4 (1.7) | 0.65 | 5 (1.3) |
| Infection | 1 (0.7) | 0 (0.0) | 0.39 | 1 (0.3) |
| Surgery | 30 (19.6) | 16 (6.7) | 0.000 | 46 (11.7) |
| Clinical trial participation | 0 (0.0) | 2 (0.8) | 0.52 | 2 (0.5) |
| Lost to follow-up | 1 (0.7) | 2 (0.8) | 1.00 | 3 (0.8) |
| Deceased | 0 (0.0) | 4 (1.7) | 0.16 | 4 (1.1) |
| Other | 14 (9.2) | 40 (16.7) | 0.04 | 54 (13.8) |
| Unknown | 4 (2.6) | 11 (4.6) | 0.42 | 15 (3.8) |

*P* values reflect comparison of patients with ulcerative colitis and Crohn's disease by $\chi 2$ test for each cause of discontinuation. The same patient can appear in more than 1 category due to competing causes of discontinuation.

at diagnosis if the index endoscopy was performed at a different hospital. Although we have tried to handle this through manual scrutiny of patient files, this explains the missing data on disease extent in a subpart of the cohort. Third, it may be seen as a limitation that disease extent subject to analysis in the present study corresponds to the extent at time of diagnosis rather than at time of exposure. Fourth, the number of hospitalizations during the study period was not recorded systematically, so any change in hospitalization pattern could not be assessed. Fifth, the categorization into remission or poor response was based on physicians ticking a box when deciding to discontinue treatment for the patient. Finally, in relation to investigative practice, we know that the use of magnetic resonance enterography (MRE) has increased during the study period, although the magnitude of such use was not measured. The increasing use of MRE is expected to result in increased identification of cases with mild disease, hence not explaining the increasing use of biological therapy during the study period.

We observed that age at first IFX exposure decreased in patients with UC during the study period, whereas this was not the case in CD. On the other hand, patients with CD were exposed to IFX after increasingly shorter disease duration during the study period, whereas a similar finding in UC did not reach statistical significance. As a possible accumulation of patients ready for IFX treatment in the beginning of the study period was not apparent, our observations seem to reflect a genuine change in prescription patterns during the period.

We observed no change in indications for treatment, in terms of acute severe vs chronically active UC and luminal vs fistulizing CD during the study period, which is in line with the fact that there has been no change in recommendations for treatment of the subgroups of the diseases. However, patients tended to be treated for less extensive disease in the last part of the study period. This was the case in both UC and CD and appears to reflect a change in prescription patterns toward treatment with IFX at an earlier stage of disease in patients with less extensive disease.

Also, time to discontinuation changed over time, at least in patients with UC, with increasing treatment duration during the observation period. Desai et al.[24] showed that patients older than 60 years of age were more likely to discontinue therapy within the first year than younger patients. As our population of UC patients was increasingly younger at first exposure, they may have been less likely to discontinue therapy. However, the increasing time to discontinuation may also reflect a tendency in clinical practice toward 1-year continuation of IFX treatment in patients with UC rather than just induction therapy. Overall, we observed several reasons for discontinuation of IFX treatment, remission being the cause in 30%–40% of patients, hence resembling remission rates reported by Schnitzler et al. in 2009 from a single-center cohort study of 614 patients.[8] It has been speculated that decreasing surgery rates in patients with UC during the same period relate to IFX treatment, but this remains uncertain.[22]

In patients with CD, the mean treatment duration was more stable during the study period and longer than the mean time in patients with UC (around 3 years vs 1 year), which remains unexplained. In contrast to our finding of 50% of CD patients discontinuing treatment after 3 years, Pressman et al.[23]

reported that 80% discontinue after 3 years. While Pressman and colleagues' study was conducted during the earlier part of our study period, we observed a stable time to discontinuation during the entire period. This may partly be due to a lower frequency of adverse events in our study as compared with several[10, 15, 20] but not all previous studies.[21] The lower frequency may be explained by better dose adjustment, a single and experienced center serving a whole region, or other yet unknown factors. Overall, the number of real-life long-term studies on use of biologics in IBD is limited, which minimizes the potential for comparison of the present findings with existing literature.

In conclusion, our unselected cohort study revealed a decrease in age of UC patients and a decrease in duration of CD at the time of first IFX exposure during the initial 16 years of observation postmarketing. Further, we observed a significant change toward less extensive disease in both CD and UC patients exposed to IFX and an increasing time to discontinuation in patients with UC in recent years. This indicates that prescription patterns have changed since IFX was introduced to the market. Better knowledge of and experience in using biological therapies, less hesitation in prescribing IFX to a broader range of patients, and reduction in costs of IFX may to some extent explain our findings. However, determining the causes of these changes requires further studies.

## ACKNOWLEDGMENTS

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# Paper III: Premedication With Corticosteroids Does Not Impact Pharmacokinetics of Infliximab in IBD Irrespective of Azathioprine Co-Treatment

# Premedication with corticosteroids does not impact the pharmacokinetics of infliximab in inflammatory bowel disease irrespective of azathioprine cotreatment

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**Objective** Loss of infliximab (IFX) effect is a clinical challenge in the management of patients with Crohn's disease (CD), but this can potentially be reduced with azathioprine (AZA) or with corticosteroids (CS). We aimed to study whether CS premedication with or without cotreatment with AZA could reduce antibody formation and affect the IFX elimination rate.

**Patients and methods** A cross-sectional observational study was conducted at two centers with CD patients receiving maintenance IFX therapy for 12–18 months. In addition to IFX, patients received either CS premedication or not, with or without concominant AZA.

**Results** Fifty-seven patients were included in the study. Thirty-one patients received premedication with CSs, and 11 (35.5%) of these also received AZA, whereas this was the case for 22 of 26 (84.6%) patients in the non-CS group. No difference in IFX trough level ($P = 0.10$) or halftime elimination ($P = 0.31$) was observed with or without CS premedication. Concomitant AZA was associated with significantly longer mean half-life of IFX ($P = 0.04$). Total IFX antibody concentrations were 15.8 and 12.9 with and without CS, respectively, in those not receiving AZA versus 4.3 and 6.1 AU/ml with and without CS, respectively, in those receiving AZA ($P = 0.004$). Premedication with CS did not have any effect on the frequency of antibody formation ($P = 0.28$).

**Conclusion** In patients with CD and in maintenance IFX therapy, premedication with CS did not influence antibody formation, IFX trough levels or IFX halftime elimination, irrespective of concomitant AZA use. However, the use of AZA was associated with higher IFX trough levels and lower total IFX antibody concentrations. Eur J Gastroenterol Hepatol 00:000–000


## Introduction

Infliximab (IFX) is an effective treatment for Crohn's disease (CD). IFX is a chimeric tumour necrosis factor (TNF)-α antibody consisting of 25% nonhuman (murine) protein, which in patients has been shown to cause the formation of IFX antibodies in up to 30% of patients [1]. This can lead to a reduced/or loss of anti-inflammatory effect [2–6].

Several studies have demonstrated that combined therapy with IFX and azathioprine (AZA) reduces antibody formation [3,7], but it has been questioned whether preinfusion premedication with corticosteroids (CS) can reduce the formation of IFX antibodies. Hence, in a randomized placebo-controlled trial in patients with CD, Farrell *et al.* [8] showed that 200 mg of hydrocortisone on the day of IFX infusion led to significantly less antibody formation towards IFX.

Studies conducted within the field of rheumatology have shown diverging conclusions [9–19], and a role for prophylactic CS in IFX therapy has so far not been established.

The purpose of this study was to investigate whether CS premedication with or without AZA comedication during IFX therapy could affect the frequency of IFX antibody formation, trough levels and the elimination rate of IFX.

## Patients and methods

### Study population

Patients with CD who received IFX maintenance therapy were included at two Danish centers between 2015 and 2017. All patients had a well-established diagnosis of CD and received IFX therapy for 12–18 months. All patients were naive to biological therapy at the initiation of the treatment and were selected as a trans-sectional cohort to participate consecutively in the study. The inclusion criteria were as follows: CD, age above 18 years, and maintenance IFX treatment for 12–18 months.

Disease extent, disease behavior, prior history of surgery, family history, and smoking habits were registered.

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Keywords: antibodies, Crohn's disease, infliximab, premedication

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### Premedication

The premedication with CS consisted of 40 mg of prednisolone orally on the day before IFX therapy and 40 mg of methylprednisolone (SoluMedrol, Pfizer, Denmark) intravenously on the day of IFX infusion.

### Comedication

All patients on AZA therapy had been on a stable dose for at least 3 months at a dose of 1.5–2.5 mg/kg.

### Samples

After inclusion of a patient, blood samples were obtained at the next scheduled IFX infusion for IFX concentrations before IFX infusion (trough level), 1 h after IFX infusion ended (peak-level) and 1 week after IFX infusion. IFX antibody concentration was measured before IFX infusion.

### Laboratory tests

#### Infliximab concentration

A two-step immunoassay based on ELISA technique measured IFX concentration in human serum. All samples were tested as duplicates. The result was determined by the development of chemiluminescence in the terminal phase.

The following procedure was done on blood samples obtained just before IFX infusion, time = 0: TNF-α (1 mg/ml) (Tebu-Bio., Roskilde, Denmark) coated – and saturated with PBS containing 1% bovine serum albumin. Microtiter 96-well plates (Nunc C8 white MaxiSorp; Fisher Scientific Labosi, Elancourt, France) were washed four times with PBS tween (PBS pH 7.2 + 0.05% Tween 20) before 100 µl diluted (1 : 100/1 : 800) patient sample was added. The plates were incubated 2 h at 37°C, followed by four times wash with PBS Tween. A conjungate, Fc-specific alkaline phosphatase (Sigma-Aldrich, Saint-Quetin-Fallavier, France) linked goat antihuman-IgG was added, and the plates were left for 1 h shaking incubation at room temperature. Once more, the plates were washed four times with PBS Tween before two times wash in assay buffer (Applied BioSystems, Foster City, California, USA).

Substrate chemiluminescent alkaline phosphatase (Applied BioSystems) 100 µl was added and incubated for 10 min at room temperature in darkness. The chemiluminiscence reaction (FluoStar Optima with MARS data analysis software; Ramcon, Birkeroed, Denmark) was read as relative units of light. The relative units of light and the concentration of IFX are proportional. The limit of detection was 0.5 µg/ml.

The same procedure, as described above, was used for the postinfusion samples, but patient samples were further diluted to 1 : 5000/1 : 10 000/1 : 20 000.

#### Total human antibodies against infliximab

Blood samples before infusion: IDK monitor (Immundiagnostik AG, Stubenwald-Allee, Bensheim, Germany) IFX total ADA ELISA is a CE-branded test based on the ELISA principle. The test determined human antibodies against TNF-α blocker IFX in the presence of IFX in plasma, that is, a drug-tolerant assay. 'Total' ADA refers to the measurement of both free and bound antibodies against IFX.

### Statistical analyses

Linear regression was used to test for differences in trough values, peak values and $t_{1/2}$ of IFX concentrations, and trough values of IFX antibody concentrations between the ± CS premedication groups. Furthermore, we tested for possible interaction between the ± CS groups and ± concomitant AZA treatment.

We applied the logarithmic transformation to the IFX concentrations and antibody concentrations in order to obtain normal distributed data and therefore geometric means and coefficients of variation were reported. This was not the case for IFX $t_{1/2}$, as these data were normal distributed. For IFX $t_{1/2}$, means and standard deviations were reported.

The assumption of normality was checked by inspection of QQ-plots.

### Ethical considerations

All patients gave informed consent. The study was approved by the Regional Ethics Committee (N-20140003) as well as by the Danish Data Protection Agency (2008-58-0028).

## Results

### Patient characteristics

From 2015 to 2017, 57 CD patients were included in the study. Two patients failed to show up for the one-week blood sampling. Patient characteristics are shown in Table 1. Twenty-two (84.6%) – CS patients were on concomitant immunomodulatory therapy, while this was the case for 11 (35.5%) + CS patients.

Overall, 59.6% were female individuals. The two patient groups were comparable (Table 1).

### Infliximab concentrations

The geometric mean trough levels were 5.1 and 7.3 µg/ml for – CS and + CS patients, respectively ($P = 0.10$). Likewise, there was no difference in the geometric mean peak concentrations: 263.8 µg/ml for – CS and 285.3 µg/ml for + CS patients ($P = 0.48$), or the 1-week-after concentrations: 104.4 µg/ml for – CS and 114.0 µg/ml for + CS patients ($P = 0.63$). Box plots of the different concentrations are shown in Fig. 1. In patients with concomitant AZA, the trough level was significantly higher ($P = 0.02$, Table 2).

### Infliximab elimination rate

The mean half-life of IFX was 10.5 days in both groups (minimal 5.4 and 5.4 days and maximal 19.1 and 17.5 days for + CS and – CS, respectively). There was no difference between the two administration methods ($P = 0.31$). For individual elimination curves (Fig. 2).

However, concomitant AZA was associated with significantly longer mean half-life of IFX ($P = 0.04$; Table 2).

### Infliximab antibody concentrations

The mean total IFX antibody concentration was 10.0 AU/ml in + CS patients and 6.7 AU/ml in – CS patients ($P = 0.28$). Patients without AZA therapy had a significantly higher IFX antibody concentration ($P = 0.004$; Table 2).

**Table 1.** Patient characteristics

| Treatment (*N*) | −Corticosteroid (26) | +Corticosteroid (31) | Total (57) |
|---|---|---|---|
| Female individuals [*n* (%)] | 16 (61.5) | 18 (58.1) | 34 (59.6) |
| Age at time of study [mean (SD)] | 33.3 (13.8) | 31.6 (11.8) | 32.4 (12.7) |
| Weight [mean (SD)] (kg) | 75 (13.5) | 80.5 (21.5) | 78.0 (18.4) |
| Height [mean (SD)] (cm) | 171.6 (9.6) | 172.8 (8.9) | 172.4 (9.1) |
| Smoking at diagnosis [*N* (%)] | 5 (20.8) | 4 (12.9) | 9 (16.4) |
| Family history of inflammatory bowel disease [*N* (%)] | 5 (21.7) | 4 (12.9) | 9 (16.7) |
| Concomitant medication [*N* (%)] | 22 (84.6) | 14 (45.2) | 36 (63.2) |
| Azathioprine | 22 (84.6) | 11 (35.5) | 33 (57.9) |
| 6-Mercaptopurine | 0 (0) | 3 (9.7) | 3 (5.3) |
| Previous surgery [*N* (%)] | 5 (19.2) | 8 (27.6) | 13 (23.6) |
| Disease extent [*N* (%)] | 26 (100) | 31 (100) | 57 (100) |
| Colon | 8 (30.8) | 19 (61.3) | 27 (47.4) |
| Ileocolonic | 15 (57.7) | 9 (29.0) | 24 (35.1) |
| Small bowel | 2 (7.7) | 3 (9.7) | 5 (8.8) |
| Upper gastrointestinal | 1 (3.9) | 0 (0) | 1 (1.7) |
| Disease behaviour [*N* (%)] | 26 (100) | 31 (100) | 57 (100) |
| Nonstricturing, nonfistulizing | 16 (61.5) | 19 (61.3) | 35 (61.4) |
| Fistulizing, nonstricturing | 5 (19.2) | 11 (35.5) | 16 (28.1) |
| Stricturing, nonfistulizing | 5 (19.2) | 1 (3.2) | 6 (10.5) |
| Infliximab interval, 5 mg/kg every 4-10 weeks [mean (minimum–maximum)] | 7.65 (6–10) | 7.23 (4–10) | 7.42 (4–10) |

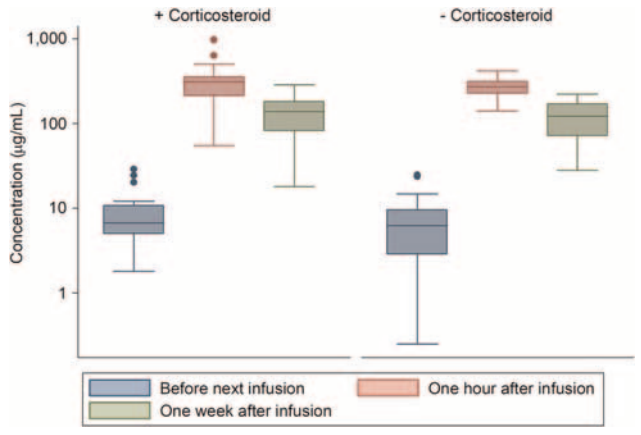


**Fig. 1.** Log concentrations of infliximab.

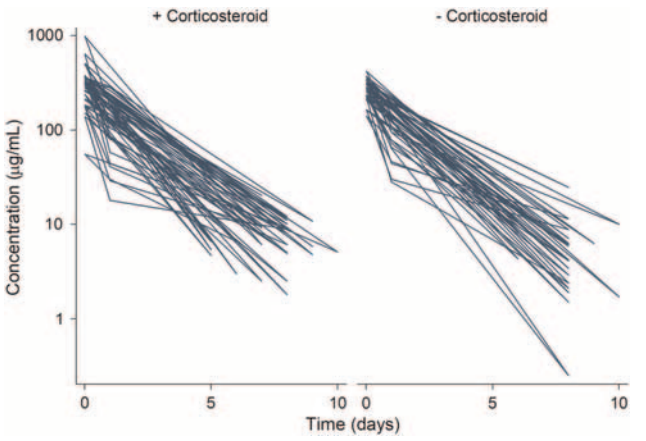


**Fig. 2.** Elimination of infliximab by each individual.

**Table 2.** Distribution of infliximab trough levels, half-life and total infliximab antibody concentrations according to premedication

| | −Corticosteroid | | +Corticosteroid | |
|---|---|---|---|---|
| Treatment (*N*) | Azathioprine (22) | No AZA (4) | Azathioprine (11) | No AZA (20) |
| Trough levels [geometric mean (CV)] (µg/ml)* | 5.97 (1.27) | 2.19 (0.76) | 9.14 (1.42) | 6.44 (2.55) |
| Half-life [mean (SD)] (days)** | 10.8 (3.2) | 8.7 (0.6) | 11.7 (2.5) | 9.9 (3.2) |
| Total IFX antibody concentrations [geometric mean (CV)] (AU/ml)*** | 6.1 (1.58) | 12.9 (0.76) | 4.3 (1.42) | 15.8 (2.55) |

AZA, azathioprine; CV, coefficient of variation; IFX, infliximab.
*$P = 0.023$, trough values higher with AZA.
**$P = 0.04$, half-life longer with AZA.
***$P = 0.004$, IFX antibody concentrations lower with AZA.

Twenty-two (38.6%) patients had detectable total IFX antibodies (cutoff >10 AU/ml). Of them, 15 (68.2%) were in the +CS group, and seven (31.8%) were in the −CS group.

## Discussion

In this cross-sectional observational study of patients with CD receiving IFX with or without comedication with AZA for at least a year, we evaluated the effect of premedication with CS.

Our data did not demonstrate any effect of CS premedication with regard to the frequency of IFX antibody formation, trough levels, and the elimination rate of IFX, whereas concomitant AZA therapy reduced the concentration of IFX antibodies. Besides, we found significantly higher trough values of IFX and longer IFX half-life in patients who received AZA therapy.

The question is relevant, as antibody formation towards anti-TNF biologics and loss of effect represent a therapeutic challenge in the clinical management of inflammatory bowel disease patients. Therefore, it was important to investigate

the theoretical presumption that premedication with CS would diminish the formation of IFX antibodies. Another study has addressed the question of premedication with CS as a modulator of immunological reactions.

In a randomized placebo-controlled trial in patients with CD, Farrell *et al.* [8] showed that 200 mg of hydrocortisone on the day of IFX infusion led to significantly less antibody formation towards IFX. However, it did not eliminate the antibody formation or infusion reactions. In contrast, in a recent retrospective study from Gold *et al.* [20], premedication use was not effective in reducing acute IFX reactions.

The findings concerning the effect of AZA are in accordance with the SONIC trial and are also in accordance with the results described by Fasanmade and colleagues [21,22].

This study has several strengths. First, to our knowledge, this is the first study evaluating steroid premedication after 12–18 months' IFX treatment in a prospective manner. Second, the study is standardized in the timing of the blood sampling.

The study also has potential limitations, which should be considered. First, the small sample size makes it possible that a small effect of CS premedication might have been overlooked. However, the results did not even indicate a trend towards an effect of CS premedication. Second, the patients in this study received maintenance IFX therapy for a minimum of 12 months, which might cause a selection bias. Hence, patients who were able to participate in the study were able to tolerate the treatment (cessation of IFX treatment due to side effects or intolerance was not registered).

### Conclusion

This study did not find any effect of CS premedication on TNF-antibody production irrespective of concomitant AZA treatment. However, we did observe a positive effect of AZA with regard to a reduced production of TNF antibodies. Thus, this study strengthens the argumentation for comedication with AZA in patients on IFX therapy, but it does not support the use of premedication with CS.

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### Conflicts of interest

There are no conflicts of interest.

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